Journal of Antimicrobial Chemotherapy (2008) **62**, 895–904
doi:10.1093/jac/dkn311
Advance Access publication 1 August 2008

JAC

Tigecycline for the treatment of multidrug-resistant Enterobacteriaceae: a systematic review of the evidence from microbiological and clinical studies

Theodoros Kelesidis[1,2], Drosos E. Karageorgopoulos[1], Iosif Kelesidis[1,3] and Matthew E. Falagas[1,4,5]*

[1]Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece; [2]Department of Medicine, Caritas St Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA, USA; [3]Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, NY, USA; [4]Department of Medicine, Henry Dunant Hospital, Athens, Greece; [5]Department of Medicine, Tufts University School of Medicine, Boston, MA, USA

Received 4 April 2008; returned 8 May 2008; revised 2 July 2008; accepted 6 July 2008

***Objectives*: Antimicrobial drug resistance is spreading among Enterobacteriaceae, limiting the utility of traditionally used agents. We sought to systematically review the microbiological activity and clinical effectiveness of tigecycline for multidrug-resistant (MDR) Enterobacteriaceae, including those resistant to broad-spectrum β-lactams due to the expression of extended-spectrum β-lactamases (ESBLs), AmpC enzymes and carbapenemases (including metallo-β-lactamases).**

***Methods*: PubMed was searched for articles including relevant data.**

***Results*: Twenty-six microbiological and 10 clinical studies were identified. Tigecycline was active against more than 99% of 1936 *Escherichia coli* isolates characterized by any of the above resistance patterns (including 1636 ESBL-producing isolates) using the US Food and Drug Administration (FDA) breakpoint of susceptibility (MIC $\leq$ 2 mg/L). Findings were not different using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint ($\leq$1 mg/L). Susceptibility rates for *Klebsiella* spp. with any of the above resistance patterns were 91.2% for 2627 isolates by the FDA criteria and 72.3% for 1504 isolates by the EUCAST criteria (92.3% for 2030 and 72.3% for 1284 ESBL-producing isolates, by the FDA and EUCAST criteria, respectively). The degree of microbiological activity of tigecycline against 576 MDR *Enterobacter* spp. isolates was moderate. In clinical studies, 69.7% of the 33 reported patients treated with tigecycline achieved resolution of an infection caused by a carbapenem-resistant or ESBL-producing or MDR Enterobacteriaceae.**

***Conclusions*: Tigecycline is microbiologically active against almost all of the ESBL or MDR *E. coli* isolates and the great majority of ESBL or MDR *Klebsiella* spp. isolates. Further evaluation of its clinical utility against such resistant Enterobacteriaceae, particularly regarding non-labelled indications, is warranted.**

Keywords: glycylcyclines, *Citrobacter*, *Serratia*, *Proteus*, *Klebsiella pneumoniae*, imipenem

Introduction

The rates of antimicrobial drug resistance and particularly of multiple drug resistance are increasing among Enterobacteriaceae, thus limiting the armamentarium of potentially active antimicrobial agents.[1,2] Of particular importance are pathogens of this family that produce β-lactamases with a broad profile of substrate activity such as extended-spectrum β-lactamases (ESBLs), AmpC β-lactamases, as well as carbapenemases, including metallo-β-lactamases (MBLs).[3] Although the re-evaluation of older agents may be important,[4,5] there is clearly a need for the development of new antimicrobial agents to keep in pace with the development and spread of drug resistance mechanisms among Gram-negative bacteria.[6]

Tigecycline (formerly GAR-936), which is chemically the 9-*t*-butylglycylamido derivative of minocycline, is a member of

*Correspondence address. Alfa Institute of Biomedical Sciences (AIBS), 9 Neapoleos Street, 151 23 Marousi, Athens, Greece. Tel: +30-694-611-0000; Fax: +30-210-683-9605; E-mail: m.falagas@aibs.gr

a novel class of antibiotics, the glycylcyclines. Tigecycline generally has a bacteriostatic mode of action against a broad spectrum of aerobic and anaerobic Gram-positive (including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci) and Gram-negative organisms.[7,8] Notably, MICs of tigecycline are generally higher for Gram-negative than for Gram-positive pathogens.[8]

Regarding Enterobacteriaceae, tigecycline has shown to evade common mechanisms of acquired tetracycline resistance, such as those conferred by efflux pumps encoded by the *tet*(A–D) resistance determinants and ribosomal protection mechanisms.[9] This property can be attributed to the greater affinity of tigecycline in binding with ribosomal sites compared with tetracyclines, along with the lack of recognition of tigecycline by tetracycline efflux pumps.[10] However, *Pseudomonas aeruginosa* and Proteeae carry inherently encoded resistance-nodulation-division (RND) efflux pumps that confer decreased susceptibility to tigecycline.[8,11–13]

The role of tigecycline for the treatment of infections caused by Enterobacteriaceae with clinically significant types of antimicrobial drug resistance has not been adequately evaluated.[14] We sought to assess systematically the microbiological activity of tigecycline against Enterobacteriaceae exhibiting multidrug resistance (MDR) and evaluate the clinical evidence regarding the use of tigecycline for the treatment of infections caused by these pathogens.

Literature review

PubMed was searched applying the terms 'tigecycline' and 'GAR-936' for articles that evaluated the *in vitro* activity of tigecycline against Enterobacteriaceae (including *Escherichia coli, Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., *Shigella* spp., *Salmonella* spp., *Serratia* spp., *Yersinia* spp., *Proteus* spp., *Morganella* spp. and *Providencia* spp.) with MDR or other clinically significant resistance patterns (1999–November 2007), as well as the clinical effectiveness of tigecycline against infections caused by these pathogens (1999–April 2008). Owing to the considerable respective variability observed in biomedical literature,[15] we accepted, for the purposes of this review, an inclusive definition of MDR in Enterobacteriaceae as resistance to two or more classes of antibacterial agents among those considered as potentially effective. We considered those resistance patterns denoted by the carriage of ESBLs, hyper-production of AmpC β-lactamases, carriage of carbapenemases, including metallo-β-lactamases (MBLs), and resistance to carbapenems to be clinically significant.

Characteristics of the included microbiological studies

We reviewed 42 different studies evaluating the *in vitro* susceptibility of Enterobacteriaceae to tigecycline.[8,14,16–55] Twenty-six of these studies evaluated the *in vitro* susceptibility to tigecycline of MDR Enterobacteriaceae or Enterobacteriaceae with other types of clinically significant resistance patterns and were included in this review.[8,17–41] Eight of the 26 overall included studies involved isolates originating from North or Latin America,[25,26,28,33,37–39,41] 7 studies involved isolates originating from Europe,[17,18,21,24,32,34,40] while 3 studies involved isolates originating from Asia[23,31,36] and 1 study involved isolates originating from Australia.[20] Seven additional studies tested broader collections of pathogens retrieved in two or more continents.[8,19,22,27,29,30,35]

The microbiological methods used for the determination of the susceptibility of Enterobacteriaceae isolates to tigecycline consisted of the broth microdilution method that was used in 19 of the 26 studies included,[8,18,19,21–23,26–31,33,35,37–41] the agar dilution method in 2 studies,[23,34] the Etest in 4 studies[20,21,32,36] and the disc diffusion method also in 4 studies.[20,32,36,39] It should be noted that more than one of the above methods was used in five of the studies included.[20,21,32,36,39]

Interpretative criteria

There is discordance between the interpretative MIC breakpoints of susceptibility of Enterobacteriaceae to tigecycline issued by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (≤1 mg/L) and those approved by the US Food and Drug Administration (FDA) (≤2 mg/L).[56] In this review, 22 of the 25 included studies used primarily the FDA approved tigecycline MIC breakpoints of susceptibility or corresponding disc zone diameter breakpoints, whereas 3 studies used the EUCAST breakpoints of susceptibility[17,34,40] and in 1 study susceptibility data were reported without the application of specific breakpoints.[26] We additionally extracted susceptibility data from tables of susceptibilities with regard to both the FDA and the EUCAST breakpoints, from studies in which relevant information was available.

For the purposes of this review, we defined as adequate microbiological activity of tigecycline against a bacterial pathogen or a group of pathogens, the susceptibility of at least 90% of the isolates of the respective pathogens to tigecycline. If specific susceptibility rates were not reported in a study, we inferred the degree of the microbiological activity of tigecycline by considering the relevant MIC data, where applicable.

Susceptibility of Enterobacteriaceae to tigecycline

Cumulative data on the susceptibility to tigecycline extracted from the included studies and classified according to different resistance patterns for each pathogen are presented in Table 1. Detailed relevant data extracted from each of the included studies are presented in Table S1 available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/). Summary data are reported below.

E. coli

We reviewed 35 studies reporting the activity of tigecycline against *E. coli*.[8,14,16,18,19,21–24,26–30,32–35,37–49,51,53–55] Using the FDA approved criteria, almost all of the *E. coli* isolates that did not exhibit MDR or other types of clinically significant resistance patterns, as defined above, were found to be susceptible to tigecycline. The corresponding MIC_{90} values were between 0.25 and 1 mg/L. ESBL production among isolates of *E. coli* in the reviewed studies ranged from 1.6% to 16.2%.[8,27–30,33,37,38,44] The rate of MDR among 4014 *E. coli* isolates collected in two studies that reported relevant data was

Table 1. Cumulative susceptibility data to tigecycline per pathogen and specific resistance patterns from various studies

Pathogens according to resistance pattern	No. of studies[ref.]	Cumulative susceptibility, % (no. of isolates)	
		FDA criteria	EUCAST criteria
E. coli			
ESBL production	16[8,18,19,23,24,27–30,32–35,38–40]	99.8 (1636)	99.7 (737)
MDR	5[18,22,23,37,41]	99.0 (308)	100 (66)
decreased susceptibility to carbapenems	3[18,21,22]	100 (14)	100 (14)
Klebsiella spp.			
ESBL production	14[8,18,19,23,24,28,29,31,33–35,37–39]	92.3 (2030)	72.3 (1284)
MDR	6[18,22,23,25,37,41]	88.5 (650)	63.6 (162)
decreased susceptibility to carbapenems	6[17,18,21,22,25,36]	94.8 (402)	71.9 (231)
Enterobacter spp.			
ESBL production	4[20,24,34,40]	91.3 (69)	77.6 (49)
MDR	5[20,22,23,37,41]	52 (344)	80.3 (66)[a]
decreased susceptibility to carbapenems	3[17,21,22]	80.3 (102)	57.8 (102)

MDR, multidrug resistance.
[a]Compared with 95.5% using the FDA criteria for these pathogens.

6%.[37,41] We identified 20 studies that reported data on the susceptibility to tigecycline of *E. coli* isolates with MDR or other types of clinically significant resistance patterns, including a total of 1936 isolates.[8,18,19,21–24,27–30,32–35,37–41] Adequate microbiological activity of tigecycline was demonstrated in all of the above studies, by either the FDA or the EUCAST criteria. Susceptibility rates were 99.6% for all of the 1936 isolates with the use of the FDA criteria and 99.4% for 795 isolates, for which relevant data were available, with the use of the EUCAST criteria.

Klebsiella spp.

We reviewed 37 different studies evaluating the activity of tigecycline against *Klebsiella* spp. isolates.[8,14,16–19,21–31,33–49,52,53,55] By the FDA approved breakpoint, more than 90% of the non-MDR *Klebsiella pneumoniae* isolates and almost all of the non-MDR *Klebsiella oxytoca* isolates were found to be susceptible to tigecycline (MIC_{90} values 0.25–2 mg/L for both species). ESBL production among isolates of *K. pneumoniae* in the reviewed studies ranged from 5.3% to 52%.[8,27–29,33,35,37,38,44] We identified 23 studies that evaluated the susceptibility to tigecycline of *Klebsiella* spp. isolates with MDR or other clinically significant resistance pattern, including a total of 3046 isolates.[8,17–19,21–31,33–39,41] By the FDA criteria, adequate microbiological activity of tigecycline was shown in 18 of the 23 studies, and the susceptibility rate to tigecycline was 91.2% for 2627 isolates. By the EUCAST criteria, adequate microbiological activity of tigecycline was shown in 2 of 20 studies that reported specific relevant data;[8,17–19,21–23,25,27–29,31,33–39,41] the susceptibility rate to tigecycline was 72.3% for 1504 isolates, for which relevant data were available.

Enterobacter spp.

We reviewed 28 studies reporting the activity of tigecycline against *Enterobacter* spp.[8,14,16,17,20–24,26,28–30,33–35,37,39–43,46–49,53,55] More than 93% of the non-MDR *Enterobacter* spp. isolates were susceptible to tigecycline applying the FDA approved breakpoint of susceptibility.[8,16,26,30,35,39,42,43,46–49,53,55] We identified 11 studies that reported data on the susceptibility to tigecycline of 686 *Enterobacter* spp. isolates with multiple drug resistance or other types of clinically significant resistance pattern.[17,20–24,28,34,37,40,41] By the FDA criteria, adequate microbiological activity of tigecycline was noted in 6 of the 11 studies,[21–24,34,40] and 380/576 (66.0%) of isolates, for which specific relevant data were available, were susceptible to tigecycline.[17,20–24,34,37,40,41] By the EUCAST criteria, adequate microbiological activity of tigecycline was noted in only one study[22] out of seven studies that reported specific relevant data, and the overall susceptibility rate of 278 Enterobacter isolates identified in these studies was 73.4% (compared with 87.8%, using the FDA criteria for these seven studies).[17,20–23,34,40]

Citrobacter spp.

We reviewed 13 studies reporting the activity of tigecycline against *Citrobacter* spp.[16,22,24,26,29,34,39,42–46,49] More than 96% of the non-MDR *Citrobacter* spp. isolates were susceptible to tigecycline by applying the FDA approved breakpoint, with MIC_{90} values of 0.25–2 mg/L.[26,29,39,42,44,46,49] We identified three studies that reported data on the susceptibility to tigecycline of 46 *Citrobacter* spp. isolates with MDR or other types of clinically significant resistance pattern. The susceptibility rate to tigecycline was 95.7% with the use of the FDA criteria.[22,24,34]

Serratia spp.

We reviewed 22 studies reporting the activity of tigecycline against *Serratia* spp.[8,16,20–22,26,28,29,33–35,39,41–49,55] More than 90% of the non-MDR *Serratia* spp. isolates were susceptible to tigecycline, by the FDA breakpoints, in all studies, with MIC_{90} values of 1–4 mg/L.[8,16,26,29,33,35,39,43–49,55] We identified six studies that reported data on the susceptibility to tigecycline of 90 *Serratia* spp. isolates with multiple drug resistance or other

types of clinically significant resistance patterns.[20–22,28,34,41] Adequate microbiological activity of tigecycline was noted in three of these six studies, using the FDA criteria,[21,22,34] and the susceptibility rate to tigecycline was 78.4% for 51 isolates, for which specific relevant data were available.

Proteeae

We reviewed 14 studies that evaluated the activity of tigecycline against species of the tribe of Proteeae and more specifically against 1890 isolates of *Proteus mirabilis* and 1032 strains of the indole-positive Proteeae (including 183 isolates of *Proteus vulgaris*, 264 isolates of *Morganella* spp. and 238 isolates of *Providencia* spp).[16,26,29,30,34,39,40,42–46,53,55] In the majority of these studies, the MIC_{90} values for Proteeae was 4–8 mg/L and most of the isolates had intermediate susceptibility to tigecycline, by the FDA breakpoints (MIC of 4 mg/L).[16,26,39,42–46] We identified two studies that reported specific data on the susceptibility to tigecycline of ESBL- or AmpC-producing isolates (Table S1 available as Supplementary data at JAC Online, http://jac.oxfordjournals.org/).[34,40]

Clinical effectiveness of tigecycline for infections caused by MDR Enterobacteriaceae

Tigecycline has been evaluated for the treatment of complicated intra-abdominal infections, in comparison to imipenem/cilastatin,[57–59] as well as in complicated skin and skin structure infections in comparison to the combination of vancomycin plus aztreonam.[9,53,60] The findings regarding the use of tigecycline in these two types of infections were favourable, leading to the approval of this agent by the FDA and the European Medicines Agency for both the above indications. Tigecycline has also been evaluated for the treatment of community-acquired pneumonia[61] and nosocomial pneumonia, as well as for the diabetic foot infections, including osteomyelitis.[40]

We identified 10 studies evaluating the clinical effectiveness of tigecycline for the treatment of patients with infections caused by MDR Enterobacteriaceae or Enterobacteriaceae with other types of clinically significant resistance.[62–71] Data extracted from these studies are presented in Table 2. The 10 studies included present data on 33 cases of patients with infections caused by MDR Enterobacteriaceae (identified as *K. pneumoniae*, *E. coli* or *Enterobacter* spp.). The types of infections reported were complicated intra-abdominal infections (including complicated pelvic infections) in 16 of the 33 patients (48.5%), bacteraemia in 8 patients (24.2%), while 6 other patients had pulmonary infection and 3 patients had a urinary tract infection. Tigecycline was administered as monotherapy in 23 patients and in combination with other microbiologically active agents in 7 cases;[63,65,66,68] relevant data were not reported for 3 patients.[64]

A favourable outcome of the infection was observed in 23 of the overall 33 included patients (69.7%), while clinical response was deemed uncertain in 3 additional cases. In 1 of the 23 patients with resolution of the infection, two recurrences of empyema occurred along with an associated rise in the tigecycline MIC from 0.75 to 2 mg/L during the course of treatment, but re-treatment was successful.[65] It should also be mentioned that among the 26 patients with a favourable or uncertain outcome of the infection, prolonged administration of tigecycline (over 21 days) was required in 5 patients. In four of those, delayed (more than 3 days) microbiological clearance or recurrence of the infecting pathogens was observed.[65,66,68,70] Finally, the tigecycline MIC for the infecting pathogens was more than 2 mg/L (the FDA breakpoint of susceptibility) in 2 of the 10 cases in which specific relevant data were reported.[68] In both these cases, the clinical outcome was characterized as uncertain.

Further considerations

In this review, potent microbiological activity of tigecycline was shown for *E. coli* isolates with MDR or other clinically significant resistance patterns (mostly production of ESBLs) by the use of either the FDA or the EUCAST breakpoints of susceptibility. Regarding ESBL-producing *Klebsiella* spp. isolates with the same as above resistance characteristics, adequate microbiological activity of tigecycline was shown with regard to the FDA criteria, but susceptibility rates fell below 90% with the use of the more conservative EUCAST criteria. Susceptibility rates to tigecycline for carbapenem-resistant *Klebsiella* spp. isolates were not lower compared with ESBL-producing ones, potentially suggesting that porin loss, which is a common mechanism contributing to carbapenem resistance in this species, may not appreciably affect the activity of tigecycline,[17] although it may relate to decreased susceptibility to other antibacterial agents apart from β-lactams.[72] Tigecycline manifested a moderate degree of antimicrobial activity against MDR *Enterobacter* spp. isolates. The small number of isolates of other species of Enterobacteriaceae identified in the included studies (*Citrobacter* spp., *Serratia* spp. and *Proteus* spp.) does not allow for safe conclusions to be drawn regarding the microbiological activity of tigecycline.

The different methodologies used in the included studies for the determination of microbial susceptibility to tigecycline should be taken into consideration. Specifically, although the majority of the included studies were entirely or partly based on the broth microdilution method for the determination of susceptibility to tigecycline, five studies did not use this method. Specifically, three studies used the Etest along with the disc diffusion method,[20,32,36] while two other studies used the agar dilution method.[23,34] The reproducibility of findings regarding susceptibility to tigecycline of Enterobacteriaceae with the use of different microbiological methods has not been adequately evaluated. Yet, it appears that the Etest provides concordant findings compared with other methods.[32,54,73] Regarding broth microdilution, it has been shown that the use of aged media (more than 12 h) may result in relative loss of the activity of tigecycline due to oxidation and thus in falsely higher MIC values.[26,74] It is plausible that some of the earlier studies included in this review (performed prior to 2005) may not have taken this issue into consideration.

Randomized controlled trials have proven the effectiveness of tigecycline for complicated intra-abdominal infections and complicated skin and skin structure infections. Whether the observed microbiological activity of tigecycline against most of the Enterobacteriaceae with the various patterns of resistance evaluated in this review is translated into clinical effectiveness for off-label indications cannot be well established on the basis of the available clinical evidence.[14] Although some experimental animal data support the above assumption,[16,75] relevant clinical

Table 2. Clinical use of tigecycline for the treatment of infections caused by Enterobacteriaceae with clinically significant resistance patterns

Author, publication year, type of study	Patient characteristics	Type of infection	Type of pathogens; resistance characteristics (tigecycline MIC)	Dose and duration of tigecycline	Concomitant antimicrobials	Outcomes
Respiratory tract infections						
Anthony 2008[68] (retrospective case series)	63-year-old female with history of cancer	tracheobronchitis	AmpC-producing *E. cloacae* with tigecycline MIC of 3 mg/L	standard dosing for: 8 days	none	clinical response uncertain; death (unrelated to infection)
	57-year-old male solid organ transplant recipient	ventilator-associated pneumonia with empyema	ESBL- and carbapenemase (KPC)-producing *K. pneumoniae* with tigecycline MIC of 1.00 mg/L	16 days	gentamicin	no clinical response; death
	69-year-old female with diabetes	nosocomial pneumonia	MDR *K. pneumoniae* with tigecycline MIC of 0.75 mg/L	11 days	none	good clinical response
	69-year-old male	aspiration pneumonia	ESBL-producing *K. pneumoniae* with tigecycline MIC of 0.75 mg/L	15 days	inhaled tobramycin	good clinical response
Daly 2007[65] (case report)	49-year-old woman with history of multiple infections due to anastomotic leak after gastric bypass surgery	nosocomial pneumonia and empyema	carbapenemase (KPC)-producing *K. pneumoniae* with tigecycline MIC of 0.75 mg/L	standard dosing for 5 weeks	ciprofloxacin	resolution of infection; recurrence of empyema; resolution after re-treatment; death during hospitalization; increase in tigecycline MIC of 2 mg/L
Knueppel 2007[66] (case report)	46-year-old man who underwent CABG after myocardial infarction	pneumonia	carbapenem-resistant *K. pneumoniae*	standard dosing for 29 days	polymyxin B	positive blood cultures for *K. pneumoniae* with same resistance profile after 2 weeks of therapy; resolution of infection

Continued

Table 2. *Continued*

Author, publication year, type of study	Patient characteristics	Type of infection	Type of pathogens; resistance characteristics (tigecycline MIC)	Dose and duration of tigecycline	Concomitant antimicrobials	Outcomes
Sepsis/bacteraemia/endovascular infections						
Anthony 2008[68] (retrospective case series)	44-year-old male heart transplant recipient	endovascular infection with recurrent bacteremia	ESBL-producing *K. pneumoniae* with tigecycline MIC of 1.50 mg/L	standard dosing for 23 days plus 18 days (recurrence)	meropenem, colistin (recurrence)	no clinical response; death
	53-year-old male with diabetes, congestive heart failure under haemodialysis	bacteraemia (septic thrombophlebitis due to retained venous catheter)	carbapenemase (KPC)-producing *E. coli* with tigecycline MIC of 0.75 mg/L	standard dosing for 133 days	none	uncertain clinical response
Souli 2008[69] (retrospective case series)	74-year-old male with diabetes, chronic renal failure and soft tissue infection receiving mechanical ventilation	breakthrough primary bacteraemia	MBL (VIM-1)-producing, colistin-resistant *K. pneumoniae* with tigecycline MIC of 0.5 mg/L	50 mg twice daily for 4 days	none	death
Cobo 2008[63] (case report)	66-year-old man who underwent CABG after acute coronary syndrome	persistent bacteraemia (for 30 days) probably due to septic thrombophlebitis	MBL (VIM-1)-and ESBL (SHV-12)-producing *K. pneumoniae* with tigecycline MIC of 0.5 mg/L	standard dosing for 24 days	colistin initially followed by 9 days of tigecycline monotherapy	resolution of infection
Knueppel 2007[66] (case report)	80-year-old man with diabetes mellitus and end-stage renal disease on haemodialysis	persistent bacteraemia for 7 days	highly drug-resistant *K. pneumoniae*	standard dosing for 22 days	polymyxin B	resolution of infection
Cunha 2007[64] (clinical trial)	3 patients	bacteraemia	MDR *K. pneumoniae* susceptible to tigecycline	standard dosing	NA	resolution of infection in 3/3 patients
Intra-abdominal infections						
Anthony 2008[68] (retrospective case series)	49-year-old female solid organ transplant recipient	pelvic abscess	AmpC-producing *E. cloacae* with tigecycline MIC of 3 mg/L	standard dosing for 7 days	none	uncertain clinical response; death (unrelated to infection)
Oliva 2005[67] (Phase 3, double-blind RCT)	13 adults	complicated intra-abdominal infections	6 ESBL-producing *E. coli*; 7 ESBL-producing *K. pneumoniae*; All susceptible to tigecycline, (MIC$\leq$1 mg/L)	standard dosing for $\geq$5 to $\leq$14 days	none	eradication or presumed eradication of infecting strains; 5/6 (83%) *E. coli*; 5/7 (71%) *K. pneumoniae*

Babinchak 2005[62] (pooled analysis of 2 Phase 3, double-blind RCTs)*	2 adults	complicated intra-abdominal infections	*E. coli* or *K. pneumoniae*, susceptible to tigecycline (MIC≤1 mg/L)	standard dosing for ≥5 to ≤14 days	none	Eradication or clinical cure in 2/2 (100%)
Urinary tract infections						
Anthony 2008[68] (retrospective case series)	64-year-old male with diabetes	urinary tract infection	ESBL-producing *K. pneumoniae*	standard dosing for 15 days	none	no clinical response; death (unrelated to infection)
Krueger 2008[71] (case report)	25-year-old female with paraparesis, neurogenic bladder impairment, chronic renal impairment	recurrent urosepsis accompanied by bacteraemia and metastatic pulmonary infection	*E. coli* potentially ESBL-producing	13 days	none	resolution of infection
Cunha 2007[70] (case report)	elderly male	nosocomial urinary tract infection	MDR *K. pneumoniae* (MIC 2 mg/L) and *E. aerogenes* (0.5 mg/L)	200 mg iv once daily for 14 days	none	cure (eradication of *K. pneumoniae* after 5 days and of *E. aerogenes* after 12 days)

NA, not available; CABG, coronary artery bypass grafting; RCT, randomized controlled trial; standard dosing: 100 mg loading dose followed by 50 mg twice daily, intravenously.
*Data presented are the additional to those presented in Oliva 2005.[67]

reports available in this review refer to a small number of patients. The majority of these patients achieved a favourable clinical response with tigecycline treatment. In some of these cases, though, tigecycline was co-administered with other effective antimicrobials and, also, rather prolonged administration was required for the resolution of the infections in regard. The increase in tigecycline MIC during prolonged treatment was noted as a potential issue of concern in one case report. Of note, the development of resistance to tigecycline during treatment has been observed in a few cases of MDR *Acinetobacter baumannii* infections.[76–78] Decreased susceptibility to tigecycline in Enterobacteriaceae may develop as a result of overexpression of RND-type efflux pumps (e.g. of the AcrAB type).[79,80]

There is also some concern regarding the effectiveness of the use of tigecycline for the treatment of bloodstream infections. The concentrations achieved in this compartment by tigecycline, administered at the currently recommended dosage, are relatively low, not exceeding 1 mg/L,[81] a value which is lower than the FDA-approved MIC breakpoint of susceptibility. Since tigecycline achieves the maximum of its antimicrobial activity at concentrations near the MIC, the efficacy of this agent may be suboptimal if used for the treatment of bloodstream infections caused by pathogens with relatively elevated MIC.[82]

Regarding the combination of tigecycline with other antibacterial agents, which may frequently be used in routine clinical practice for the treatment of severe infections, synergy studies have revealed an indifferent effect of most studied combinations against Gram-positive or Gram-negative bacteria.[83] However, specific synergisms against certain Enterobacteriaceae have been noted, which might be worthy of further investigation. Specifically, time–kill experiments with Gram-negative pathogens confirmed synergism between tigecycline and ceftriaxone against *K. pneumoniae*, tigecycline and imipenem against *Enterobacter cloacae*, tigecycline and ceftazidime against *M. morganii*, tigecycline and trimethoprim/sulfamethoxazole against *P. mirabilis* and *Serratia marcescens*, as well as between tigecycline and amikacin against *P. mirabilis* and *P. vulgaris*.[83] Moreover, antagonistic effects of tigecycline combinations have been observed only rarely.[83]

Conclusions

The synthesis of data from relevant studies showed that tigecycline has *in vitro* activity, according to the FDA approved breakpoints of susceptibility, against more than 90% of *E. coli* or *Klebsiella* spp. isolates characterized by MDR or by-production of ESBLs or of AmpC β-lactamases or by decreased susceptibility to carbapenems. In the case of *Klebsiella* spp. isolates, susceptibility rates were appreciably lower with the use of the more conservative EUCAST breakpoints. The activity of tigecycline against a relatively small number of *Enterobacter* spp. isolates with the above-mentioned characteristics of resistance was moderate. Available clinical reports on the use of tigecycline for the treatment of infections caused by such resistant Enterobacteriaceae refer to a limited number of patients. Tigecycline treatment has been associated with resolution of the infection in the great majority of relevant reports. Since tigecycline may be one of the few microbiologically active agents against MDR Enterobacteriaceae, further well-designed studies on the clinical effectiveness of tigecycline

for infections caused by these pathogens, particularly for bacteraemia and complicated urinary tract infections, are required.

Funding

No external funding was received for this study.

Transparency declarations

None to declare.

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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