Clinical and Microbiological Outcomes of Serious Infections with Multidrug-Resistant Gram-Negative Organisms Treated with Tigecycline

Kara B. Anthony,[1,4] Neil O. Fishman,[1,4] Darren R. Linkin,[1,3,4,5] Leanne B. Gasink,[1,4,5] Paul H. Edelstein,[2] and Ebbing Lautenbach[1,3,4,5]

[1]Division of Infectious Diseases, Department of Medicine, and Departments of [2]Pathology and Laboratory Medicine and [3]Biostatistics and Epidemiology, [4]Center for Education and Research on Therapeutics, and [5]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia

Eighteen patients received tigecycline as treatment for infection due to multidrug-resistant gram-negative bacilli, including *Acinetobacter baumannii* and *Klebsiella pneumoniae* carbapenemase– and extended-spectrum β-lactamase–producing Enterobacteriaceae. Pretherapy minimum inhibitory concentration values for tigecycline predicted clinical success. Observed evolution of resistance during therapy raises concern about routine use of tigecycline in treatment of such infections when other therapies are available.

Multidrug-resistant (MDR) gram-negative bacilli like *Acinetobacter baumannii, Klebsiella pneumoniae* carbapenemase (KPC)–producing Enterobacteriaceae, and extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae present a challenge to clinicians. A new broad-spectrum glycylcycline, tigecycline [1], demonstrates in vitro activity against these organisms [2, 3]. Published clinical trial data have shown tigecycline to be effective in the treatment of complicated skin, skin-structure, and intra-abdominal infections, but few gram-negative isolates recovered in these studies were ESBL-producing Enterobacteriaceae, and none were KPC-producers or *A. baumannii* [4, 5]. The role of tigecycline in the treatment of infection due to MDR gram-negative bacilli remains undefined. We conducted a retrospective study to determine clinical and microbiological outcomes of patients treated with tigecycline for serious infections caused by these MDR gram-negative organisms.

Methods. The study was conducted at the Hospital of the University of Pennsylvania, a 725-bed, academic, tertiary care medical center in Philadelphia. All adult subjects admitted to the Hospital of the University of Pennsylvania who received ⩾48 h of treatment with tigecycline between 1 March 2004 and 30 August 2006 for treatment of an infection due to an MDR gram-negative organism (defined as resistant to agents from ⩾3 classes of antibiotics, including extended-spectrum cephalosporins, carbapenems, β-lactam/β-lactamase–inhibitor combinations, and aminoglycosides) were identified through the Hospital of the University of Pennsylvania pharmacy database. Patients receiving a full course (defined as ⩾7 days) of tigecycline treatment were included in the study. All available data (electronic medical records, laboratory data, and medication administration records) from their hospital stay—starting 6 weeks before the first dose of tigecycline through discharge—were reviewed. Established criteria were used to define clinical infection [6].

Identification and susceptibility testing of bacterial isolates were performed by standard techniques, with use of a semiautomated system (Vitek 2; bioMérieux). ESBL-producing *Escherichia coli* and *K. pneumoniae* were detected and confirmed according to Clinical Laboratory Standards Institute standards, with use of a double disk test for confirmation. AmpC- and KPC-resistance mechanisms were inferred on the basis of susceptibility patterns; in one case, KPC presence was confirmed by PCR, as described elsewhere [7, 8]. Tigecycline susceptibility was determined using the Etest method (AB Biodisk), and for purposes of this study, Clinical Laboratory Standards Institute interpretive criteria for Enterobacteriaceae were used for both Enterobacteriaceae and *A. baumannii* (susceptible MIC, ⩽2 μg/mL; intermediate MIC, >2 or <8 μg/mL; resistant MIC, ⩾8 μg/mL).

All patients received standard Food and Drug Administration (FDA)–approved dosing of tigecycline (initial loading dose, 100 mg, followed by 50 mg administered intravenously every 12 h) [1]. Clinical response at the end of treatment was defined as positive (partial or complete improvement of signs/symptoms of infection), negative (no improvement or deterioration of signs/symptoms of infection), or uncertain [9]. Microbiological response was defined as positive (sterile culture results during or after the course of antibiotic therapy), negative (persistently positive culture results with the same organism 3 days after

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Reprints or correspondence: Dr. Kara B. Anthony, University of Pennsylvania School of Medicine, Div. of Infectious Diseases, 3 Silverstein, Ste. E, Philadelphia, PA 19104 (kara.anthony@uphs.upenn.edu).

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Table 1. Demographic characteristics and clinical outcomes for 18 patients treated with tigecycline for serious infections.

Infectious organism and patient	Age, years	Sex	Primary infection	Comorbid condition(s)	LOS, days	Initial source of culture specimen	Antimicrobial susceptibility[a]
Acinetobacter baumannii							
1	80	Male	VAP	CHF, COPD, HD, ICU, STR	76	BW	COL
2	78	Female	VAP	CA	58	TA	A-S, FEP, GEN, IMP, MEM, T-S, TOB
3	59	Female	VAP	ICU, IS, SOT, STR	114	BW	AMK
4	64	Female	VAP with empyema	COPD, ICU, IS, SOT, STR	28	TA	None
5	47	Female	VAP with empyema	DM, HD, ICU, SLE	13	TA	A-S, MEM, TOB
6	54	Male	Tracheobronchitis	DM, IS, SOT, STR	5	BW	A-S, IMP, TOB
7	51	Male	Mediastinitis/ secondary bacteremia	CHF, ICU, IS, SOT, STR	16	Pericardial fluid/ blood	A-S, GEN, IMP, TOB
8	54	Female	UTI	DM	9	Urine	A-S
9	86	Female	Cellulitis	DM	16	Wound	A-S, COL
10	61	Male	Diabetic ulcer/ osteomyelitis	DM	0	Wound	COL
Enterobacteriaceae							
11	63	Female	Tracheobronchitis	CA, ICU	16	BW	…
12	49	Female	Pelvic abscess	ICU, IS, SOT, STR	11	Abscess	…
13	57	Male	VAP with empyema	ICU, IS, SOT, STR	43	BW	…
14	69	Female	Nosocomial pneumonia	DM, ICU	16	BW	…
15	69	Male	Aspiration PNA	ICU	6	Sputum	…
16	64	Male	UTI	DM	4	Urine	…
17, Course 1	44	Male	Endovascular	CHF, DM, ICU, IS, SOT, STR	0	Blood	…
17, Course 2					25	Blood	…
18	53	Male	Bacteremia	CHF, DM, HD	7	Blood	…

NOTE. AMK, amikacin; A-S, ampicillin-sulbactam; BW, bronchial washing; CA, cancer; CHF, congestive heart failure; COL, colistin; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; FEP, cefepime; GEN, gentamicin; HD, receiving hemodialysis treatment; I, intermediate (2<MIC<8 μg/mL); ICU, patient was in the intensive care unit at the time of tigecycline administration; IMP, imipenem; IS, patient was receiving immunosuppression; KPC, *K. pneumoniae* carbapenemase; LEV, levofloxacin; LOS, length of stay prior to first dose of tigecycline; MEM, meropenem; ND, not determined; PNA, pneumonia; R, resistant (MIC, ⩾8 μg/mL); S, sensitive (MIC, ⩽2 μg/mL); SLE, systemic lupus erythematosis; SOT, solid-organ transplant recipient; STR, patient received steroids for >2 weeks in the prior 30 days; TA, tracheal aspirate; TIG, tigecycline; TOB, tobramycin; T-S, trimethoprim-sulfamethoxazole; UTI, urinary tract infection; VAN, vancomycin; VAP, ventilator-associated pneumonia.

[a] Active agent(s) listed.
[b] Related or unrelated indicates relationship of death to tigecycline-treated infection.
[c] Given to treat *Pseudomonas aeruginosa,* which was also isolated in the bronchial washing.
[d] Given to treat *Staphylococcus aureus,* which was also isolated in the tracheal aspirate.
[e] Given to treat *P. aeruginosa,* which was also isolated from the wound.

initiation of antibiotic treatment), or not documented [9]. For microbiological response, if any criteria for positivity were met, the response was considered to be positive. Final disposition was defined as death related to infection (death in the setting of clinical evidence of active infection or within 5 days after the last positive culture result), death unrelated to infection (death after an episode of infection but due to causes independent of the infectious process), or survival [9]. Categorical variables were compared using the Fisher's exact test.

Results. Twenty-one patients received tigecycline therapy for ⩾48 h within our facility during the defined study period for treatment of a documented MDR gram-negative infection. Of these, 18 received a full course (⩾7 days) of therapy and were included in this study (table 1). Of the 3 patients excluded from the study; 1 was transferred to another facility during treatment; 1 received 5 days of empirical therapy and, once microbiological data were available, was switched to treatment with a targeted antibiotic; and 1 had an initial isolate found to be resistant to tigecycline, so treatment was changed to another antibiotic.

Tigecycline-susceptibility testing was performed on bacterial isolates from 16 of the 18 patients before initiation of tigecycline therapy (table 1). Of 9 *A. baumannii* isolates tested, 5 demonstrated intermediate resistance. Four (80%) of these 5 patients with pretherapy isolates only intermediately susceptible to tigecycline died (all deaths were related to infection), whereas 0 of 4 patients with pretherapy isolates susceptible to tigecycline died ($P = .048$). Among the 8 patients with non–*A. baumannii* isolates, pretherapy MIC appeared unrelated to survival.

There were 8 patients who had persistently positive culture results after initiation of tigecycline therapy; repeat testing for susceptibility to tigecycline was performed for 6 of them. Of these, patient 3 had an *A. baumannii* isolate that remained intermediately susceptible (MIC, 3.00–4.00 μg/mL), and tigecycline treatment was discontinued after 28 days, because of clinical and microbiological failure. Patient 5 had an *A. baumannii* tracheal aspirate isolate that was initially susceptible but that developed resistance during therapy (the MIC increased from 2.00 to 12.00 μg/mL after 14 days).

The 4 other patients for whom susceptibility testing was

Table 1. ***(Continued.)***

Causative organism	Resistance mechanism	Initial TIG MIC, μg/mL	Therapy duration, days	Coadministered antibiotics	Response		Final disposition[b]
					Clinical	Microbiological	
…	…	3.00 (I)	7	FEP[c]	Negative	ND	Died (related)
…	…	1.00 (S)	15	VAN[d]	Positive	Positive	Alive
…	…	3.00 (I)	28	AMK, COL	Negative	Negative	Died (related)
…	…	3.00 (I)	10	COL (inhaled)	Negative	ND	Died (related)
…	…	2.00 (S)	49	None	Positive	Positive	Alive
…	…	ND	8	TOB (inhaled)	Positive	ND	Alive
…	…	3.00 (I)/ 2.00 (S)	8	TOB	Negative	ND	Died (related)
…	…	1.00 (S)	17	None	Positive	Positive	Alive
…	…	3.00 (I)	17	LEV[e]	Positive	ND	Alive
…	…	2.00 (S)	42	None	Uncertain	ND	Alive
Enterobacter cloacae	AmpC	3.00 (I)	8	None	Uncertain	ND	Died (unrelated)
E. cloacae	AmpC	ND	7	None	Uncertain	Negative	Died (unrelated)
Klebsiella pneumoniae	ESBL, KPC (confirmed)	1.00 (S)	16	GEN	Negative	Negative	Died (related)
K. pneumoniae	Data unavailable	0.75 (S)	11	None	Positive	ND	Alive
K. pneumoniae	ESBL	0.75 (S)	15	TOB (inhaled)[c]	Positive	ND	Alive
K. pneumoniae	ESBL	ND	11	None	Negative	Positive	Died (unrelated)
K. pneumoniae	ESBL	1.50 (S)	23	None	Negative	Negative	…
K. pneumoniae	ESBL	1.00 (S)	18	MEM, COL	Negative	Negative	Died (related)
Escherichia coli	KPC (inferred)	0.75 (S)	133	None	Uncertain	Negative	Alive

repeated had bacterial isolates that remained susceptible to tigecycline during therapy. Patient 13 had persistent *K. pneumoniae* tracheal and pleural isolates, despite 7 days of tigecycline treatment (MIC, 1.50 μg/mL), and ultimately died, after 16 days of treatment, of sepsis and respiratory failure. Patient 7 had a primary *A. baumannii* mediastinitis and secondary bacteremia, with blood culture results that remained positive after 5 days of therapy, despite repeated MIC values of 2.00 μg/mL. The patient died, on day 8 of therapy, of causes related to this infection. Patient 17, a recent heart transplant recipient, developed postoperative mediastinitis and an aortic pseudoaneurysm at the allograft anastomosis, both due to *K. pneumoniae*. His blood culture results were also positive (MIC, 1.0 μg/mL), and he remained persistently bacteremic, despite >40 days of therapy. The patient ultimately died of aortic rupture. Patient 18 had multiple recurrences of *E. coli* bacteremia (MIC, <0.75 μg/mL) in the setting of a retained venous catheter and septic thrombophlebitis, despite >100 days of inpatient therapy. He was transferred to another facility, where he later died, on day 133 of therapy.

Discussion. We describe 18 patients who received tigecycline for treatment of serious infections caused by MDR gram-negative bacilli. Tigecycline was used to treat a variety of infections, many not indicated in official FDA labeling for tigecycline. Most patients were critically ill at the time of tigecycline administration, and overall clinical outcomes were poor.

Although tigecycline's potent in vitro activity against MDR gram-negative bacilli has suggested clinical success in the treatment of infections due to these organisms [3], there are few data from the clinical setting to support this. In our study, almost one-half of initial *A. baumannii* isolates showed intermediate susceptibility to tigecycline; this was associated with a higher mortality rate. This finding complements other recent reports of pre-existing reduced tigecycline susceptibilities [10] and suggests that pretherapy tigecycline MIC values may predict clinical outcome in these infections. It is important to note that no adjustment for the effect of potential confounders could be made in our analysis on the basis of our small sample size.

In addition to pre-existing tigecycline resistance among *A. baumannii,* we observed that 1 isolate acquired full resistance to tigecycline during treatment. Recent reports have similarly described the emergence of resistance among MDR gram-negative organisms during therapy and question the durability of antimicrobial activity of tigecycline as its use becomes more widespread [11–14]. Additionally, in our study, we observed persistent *A. baumannii, E. coli,* and *K. pneumoniae* bacteremia in patients receiving tigecycline treatment, despite isolates that maintained MIC values below the susceptibility breakpoint. Although at least 2 of these patients had potential sources for their persistent infection, recent reports by other groups have raised concerns about the use of tigecycline to treat bloodstream infection caused by organisms with MIC values ⩾1 μg/mL given the low mean peak serum concentrations of tigecycline that are achievable at recommended doses [11, 12]. Also of note, tigecycline was used by clinicians in our study to treat 2

urinary tract infections, despite limited excretion of tigecycline in the urine. Taken together, these observations should caution against indiscriminate use of tigecycline to treat infection with gram-negative bacilli in poorly penetrated anatomic sites, because this may promote the development of further resistance.

Although our study describes results from a small number of heterogeneous patients at a single institution, our findings should serve to generate hypotheses about the role of tigecycline in treatment of MDR gram-negative bacterial infection that can be tested in larger and more-formal studies. Additionally, our study should suggest that, until comparative data are available, more-accepted therapies like β-lactams or carbapenems [15, 16] should be used preferentially (with desensitization as needed for allergies) when susceptibility data allow. This point is especially relevant in our population, in which a majority of patients received tigecycline solely because of a β-lactam allergy but had isolates that were susceptible to ampicillin-sulbactam and/or carbapenems.

In summary, we describe the use of tigecycline as initial treatment for serious infection caused by MDR gram-negative bacilli. Our data suggest that pretherapy tigecycline MIC values in *A. baumannii* isolates may predict clinical outcome. The observed evolution of resistance in 1 *A. baumannii* isolate, as well as persistent bacteremia with several of the organisms during therapy, raises concern about the routine use of tigecycline in the treatment of these infections until more-formal comparative data are available.

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