In Vitro Activities of Tigecycline (GAR-936) against Recently Isolated Clinical Bacteria in Spain

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Received 3 August 2001/Returned for modification 15 October 2001/Accepted 3 December 2001

The antimicrobial activities of tigecycline (GAR-936) were compared with those of other agents against 1,087 strains recently isolated in 12 Spanish medical centers. Tigecycline showed activity against a wide spectrum of aerobic and anaerobic bacteria, including strains such as methicillin-resistant *Staphylococcus aureus*, coagulase-negative staphylococci, penicillin-resistant *Streptococcus pneumoniae*, *Enterococcus faecium*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*.

Tigecycline (formerly GAR-936), the 9-*t*-butylglycylamido derivative of minocycline, is a member of the new group of antibiotics, the glycylcyclines. Previous studies (3, 5–7, 9, 17) have shown that tigecycline exhibits potent activity against a broad spectrum of aerobic and anaerobic bacteria, including those containing the two major determinants of tetracycline resistance, ribosomal protection and active efflux. In vivo, tigecycline had a protective effect against acute lethal infections in mice caused by *Escherichia coli*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* (20). The efficacy of tigecycline has also been proved in a rat model of experimental endocarditis involving both methicillin-resistant *S. aureus* and vancomycin-susceptible and -resistant *Enterococcus faecalis* isolates (13). Although tigecycline, like other derivatives of tetracycline, demonstrated bacteriostatic activity, Hoellman et al. (9) showed that it was bactericidal for *S. pneumoniae* after 24 h, with significant killing rates at earlier time periods. The pharmacokinetics of tigecycline in healthy volunteers were linear. After administration of an intravenous dose of 300 mg, the maximum concentration in serum was 2.8 µg/ml and the half-life was 36 h (G. Muralidharan, J. Getsy, P. Mayer, I. Paty, M. Micalizzi, J. Speth, B. Wester, and P. Mojaverian, Abstr. 39th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-416, p. 303, 1999).

The present study was performed to evaluate the in vitro activities of tigecycline compared with those of other agents against a wide range of recent clinical isolates. A total of 1,087 clinical strains from the 14 different species groups listed in Tables 1, 2, and 3 were tested. Twelve medical centers located throughout Spain were asked to collect consecutive isolates during January and February 2001. Each participating laboratory performed routine identification to the species level and susceptibility testing on all organisms. These were then sent to the coordinating laboratory, Hospital Clínico San Carlos, Ma-

drid, Spain, in transport medium (Culturette and Anaerobic Culturette; Becton Dickinson Microbiology Systems, Sparks, Md.). Only one isolate per species per patient was included in this study. Upon receipt at the coordinating laboratory, the isolates were subcultured onto blood agar or brucella blood agar to ensure purity. Their identities were confirmed with the following commercial systems: Slidex Staph, Slidex-pneumo, Rapid ID 32 STREP, ID 32 STAPH, ID 32 GN, and Rapid ID 32A (bioMérieux, Marcy l'Etoile, France). Isolates were frozen at –70°C until processing.

Antimicrobial agents tested were obtained from their respective manufacturers. The group of antimicrobial agents tested varied according to the bacterial species. For *S. pneumoniae* susceptibility was tested by the agar dilution method with Mueller-Hinton agar supplemented with 5% sheep blood. Susceptibility testing for the remaining isolates was performed by the agar dilution method in accordance with the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS) (14–16). Production of β-lactamase was tested with nitrocefin disks (Cefinase; Becton Dickinson Microbiology Systems). Appropriate quality control was performed with *E. coli* ATCC 25922, *E. coli* ATCC 35218, *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *E. faecalis* ATCC 51229, *S. pneumoniae* ATCC 49619, *Pseudomonas aeruginosa* ATCC 27853, *Bacteroides fragilis* ATCC 25285, and *Bacteroides thetaiotaomicron* ATCC 29741. The data were analyzed with Epi Info 2000 software (version 1.1).

Table 1 summarizes the antimicrobial activities of tigecycline and the comparator agents against the gram-positive aerobic isolates tested. Among the 102 *S. pneumoniae* isolates included in the study, 62.7% were intermediate and 37.3% were highly resistant to penicillin. More than half (54.9%) were resistant to erythromycin. For three (2.9%) isolates levofloxacin MICs were 8 to 32 µg/ml. The emergence of resistance to fluoroquinolones in *S. pneumoniae* has already been reported (4, 8, 10). The MICs of tigecycline for all pneumococci, irrespective of their susceptibilities to β-lactams or macrolides, ranged from ≤0.06 to 0.125 µg/ml. These results are similar to those obtained by Petersen et al. (20). For all staphylococci tested tigecycline MICs were ≤0.5 µg/ml, and both the MIC at which

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† Members of the Spanish Group of Tigecycline are listed in the Appendix.

TABLE 1. In vitro activities of tigecycline and other antimicrobial agents against gram-positive isolates

Organism (no. of isolates) and agent	MIC (μg/ml)			% Resistant strains ^a
	Range	50%	90%	
Penicillin-intermediate and -resistant <i>S. pneumoniae</i> (102)				
Tigecycline	≤0.06–0.125	≤0.06	0.125	—
Penicillin	0.125–8	1	2	37.3
Cefotaxime	0.01–4	0.5	1	2
Erythromycin	≤0.06–256	4	128	54.9
Vancomycin	≤0.06–0.5	0.25	0.25	0
Linezolid	≤0.06–0.25	1	1	—
Quinupristin-dalfopristin	≤0.06–1	1	1	0
Levofloxacin	0.25–32	1	1	2.9
Methicillin-resistant <i>S. aureus</i> (111)				
Tigecycline	≤0.06–0.5	0.125	0.5	—
Gentamicin	≤0.06–>512	0.5	128	38.7
Rifampin	≤0.06–256	≤0.06	≤0.06	0.9
Levofloxacin	≤0.06–16	8	8	59.5
Linezolid	0.25–1	1	1	—
Quinupristin-dalfopristin	0.125–1	0.25	0.5	0
Vancomycin	0.25–1	0.5	1	0
Teicoplanin	≤0.06–2	0.5	2	0
Coagulase-negative staphy- lococci ^b (100)				
Tigecycline	≤0.06–0.5	0.125	0.5	—
Gentamicin	≤0.06–128	≤0.06	64	32
Rifampin	≤0.06–>256	≤0.06	2	10
Levofloxacin	≤0.06–128	0.25	8	26
Linezolid	0.125–1	0.25	0.5	—
Quinupristin-dalfopristin	≤0.06–1	0.125	0.25	0
Vancomycin	0.5–2	1	1	0
Teicoplanin	0.25–8	1	4	0
<i>E. faecalis</i> (52)				
Tigecycline	0.25–0.5	0.25	0.25	—
Ampicillin	1–2	1	1	0
Linezolid	0.5–1	1	1	—
Quinupristin-dalfopristin	0.125–8	4	8	75
Levofloxacin	0.25–32	1	32	36.5
Vancomycin	0.25–2	1	2	0
Teicoplanin	0.125–1	0.25	0.25	0
<i>E. faecium</i> (51)				
Tigecycline	0.125–0.25	0.125	0.25	—
Ampicillin	1–64	64	64	86.3
Linezolid	0.5–1	1	1	—
Quinupristin-dalfopristin	0.25–16	2	4	21.6
Levofloxacin	1–64	16	32	66.7
Vancomycin	0.5–1	0.5	1	0
Teicoplanin	0.25–2	0.5	1	0

^a MICs from NCCLS for resistant isolates are as follows: erythromycin, $\geq 1 \mu\text{g/ml}$; penicillin and cefotaxime, $\geq 2 \mu\text{g/ml}$; quinupristin-dalfopristin and rifampin, $\geq 4 \mu\text{g/ml}$; levofloxacin, $\geq 8 \mu\text{g/ml}$; ampicillin and gentamicin, $\geq 16 \mu\text{g/ml}$. —, breakpoints for tigecycline and linezolid are not provided by NCCLS.

^b *S. capitis* ($n = 4$), *S. chromogenes* ($n = 3$), *S. epidermidis* ($n = 69$), *S. haemolyticus* ($n = 11$), *S. hominis* ($n = 7$), *S. saprophyticus* ($n = 1$), and *S. warneri* ($n = 5$).

90% of strains are inhibited (MIC_{90}) and the range of MICs for tigecycline were slightly lower than those previously reported by Patel et al. (17) and Boucher et al. (3). Among the enterococci, tigecycline was equally active against *Enterococcus faecium* and *E. faecalis*. The activity of tigecycline against vancomycin-resistant enterococci could not be studied because the enterococcal isolates included in this study were all susceptible to vancomycin and teicoplanin. In Spain, the prevalence of

vancomycin resistance among enterococcal isolates is very low (19), in contrast to reports from the United States, where the prevalence of vancomycin resistance is about 17% (12). The MIC_{50} s and MIC_{90} s of tigecycline for enterococcal isolates ranged from 0.125 to 0.25 $\mu\text{g/ml}$. These values are similar to those reported previously (3, 6, 20). None of the *E. faecium* strains produced β -lactamase, although for 74.5% of these organisms ampicillin MICs were 64 $\mu\text{g/ml}$. High levels of resistance to gentamicin (MICs, $>500 \mu\text{g/ml}$) and streptomycin (MICs, $>2,000 \mu\text{g/ml}$) were more common among *E. faecium* isolates (21.6 and 62.7%, respectively) than among *E. faecalis* isolates (11.5 and 44.2%, respectively).

Tigecycline activities against members of the family *Enterobacteriaceae* and nonfermentative gram-negative bacilli are shown in Table 2. The tigecycline MIC_{90} s for all members of the family *Enterobacteriaceae* tested ranged from 0.5 to 2 $\mu\text{g/ml}$. Data from the SENTRY antimicrobial surveillance program study, recently performed in Europe (21), showed a high prevalence of quinolone resistance among *E. coli* strains isolated in Spain. The MICs of tigecycline were similar for ciprofloxacin-resistant and -susceptible *E. coli* strains, whereas the rate of resistance to gentamicin was significantly ($P < 0.01$) higher among ciprofloxacin-resistant *E. coli* (24.1%) strains than among ciprofloxacin-susceptible *E. coli* strains (5.4%).

Against *Acinetobacter baumannii*, an important cause of nosocomial infections, the rank order of activity of all agents tested determined by using MIC_{50} s and MIC_{90} s was as follows: polymyxin B $>$ tigecycline $>$ sulbactam $>$ levofloxacin $>$ ampicillin-sulbactam $>$ imipenem $>$ cefepime $>$ piperacillin-tazobactam $>$ gentamicin. Resistance to imipenem was detected in 28.1% of all *A. baumannii* isolates tested, and more than 90% of *A. baumannii* strains were inhibited by tigecycline at 8 $\mu\text{g/ml}$. Gales and Jones (6) reported an MIC_{90} of tigecycline for *Acinetobacter* sp. isolates of 2 $\mu\text{g/ml}$. However, they studied a smaller number of isolates ($n = 30$) than we did and included different species of *Acinetobacter* in their study.

Most clinical isolates of *Stenotrophomonas maltophilia* are inherently resistant to several antimicrobial agents, and few therapeutic options remain for the treatment of infections caused by these organisms. In this study, the most active agent against *S. maltophilia* was trimethoprim-sulfamethoxazole, to which 98.1% of strains were susceptible. The rates of resistance to piperacillin-tazobactam, ceftazidime, and amikacin were $>65\%$. Susceptibility and intermediate susceptibility to ticarcillin-clavulanate were found in 73 and 27% of *S. maltophilia* isolates, respectively. The MIC_{90} of tigecycline (4 $\mu\text{g/ml}$) was at least eightfold lower than those of ticarcillin-clavulanate, piperacillin-tazobactam, ceftazidime, and amikacin and comparable to that of trovafloxacin. To our knowledge, only two other published studies (6, 20) have reported tigecycline activity against *S. maltophilia* isolates. Our results agree with those reported in both studies. All *P. aeruginosa* isolates were susceptible to cefepime, and 6.7% were resistant to imipenem. In accordance with the data published by Gales and Jones (6) and Petersen et al. (20), tigecycline showed less activity against these organisms, and its MIC_{90} was 16 $\mu\text{g/ml}$.

The in vitro activities of tigecycline against the anaerobic isolates tested are summarized in Table 3. Members of the *B. fragilis* group are the anaerobic bacteria most frequently isolated from clinical infections, and resistance to several of the

TABLE 2. In vitro activities of tigecycline and other antimicrobial agents against gram-negative isolates

Organism (no. of isolates) and agent	MIC (μg/ml)			% Resistant strains ^a
	Range	50%	90%	
Ciprofloxacin-resistant				
<i>E. coli</i> (58)				
Tigecycline	0.5–2	1	1	—
Ciprofloxacin	4–256	16	64	100
Ampicillin	2–>256	256	>256	81
Cefotaxime	≤0.06–32	0.125	2	0
Cefepime	≤0.06–16	≤0.06	0.5	0
Amoxicillin-clavulanate	4–64	16	32	29.3
Piperacillin-tazobactam	2–256	8	16	1.7
Gentamicin	≤0.06–128	0.25	32	24.1
Ciprofloxacin-susceptible				
<i>E. coli</i> (56)				
Tigecycline	0.5–2	1	1	—
Ciprofloxacin	≤0.06–1	≤0.06	0.25	0
Ampicillin	≤0.06–>256	256	>256	60.7
Cefotaxime	≤0.06–16	≤0.06	0.125	0
Cefepime	≤0.06–4	≤0.06	≤0.06	0
Amoxicillin-clavulanate	≤0.06–64	16	32	28.6
Piperacillin-tazobactam	0.25–>256	4	8	1.8
Gentamicin	0.125–64	0.25	0.5	5.4
<i>Enterobacter</i> spp. ^b (50)				
Tigecycline	1–4	1	2	—
Ciprofloxacin	≤0.06–16	≤0.06	≤0.06	2
Ampicillin	32–>256	256	>256	100
Cefotaxime	≤0.06–>256	0.25	64	16
Cefepime	≤0.06–2	≤0.06	0.5	0
Amoxicillin-clavulanate	64–128	64	64	100
Piperacillin-tazobactam	4–256	8	128	18
Gentamicin	0.125–1	0.25	0.5	0
<i>Serratia marcescens</i> (50)				
Tigecycline	2–4	2	2	—
Ciprofloxacin	≤0.06–8	≤0.06	1	4
Ampicillin	8–>256	64	>256	100
Cefotaxime	0.125–>256	0.25	1	4
Cefepime	≤0.06–128	0.125	0.25	2
Amoxicillin-clavulanate	64–128	128	128	100
Piperacillin-tazobactam	2–256	8	16	4
Gentamicin	0.125–>256	0.5	0.5	8
<i>Citrobacter</i> spp. ^c (52)				
Tigecycline	0.25–4	0.25	0.5	—
Ciprofloxacin	≤0.06–32	≤0.06	1	7.7
Ampicillin	2–>256	32	>256	73.1
Cefotaxime	≤0.06–128	≤0.06	32	5.8

Organism (no. of isolates) and agent	MIC (μg/ml)			% Resistant strains ^a
	Range	50%	90%	
Cefepime				
Cefepime	≤0.06–1	≤0.06	0.5	0
Amoxicillin-clavulanate	4–64	32	64	71.2
Piperacillin-tazobactam	1–32	2	16	0
Gentamicin	0.125–32	0.25	0.5	5.8
<i>Klebsiella</i> spp. ^d (54)				
Tigecycline	0.125–16	0.5	0.5	—
Ciprofloxacin	≤0.06–128	≤0.06	1	5.6
Ampicillin	32–>256	64	>256	100
Cefotaxime	≤0.06–16	≤0.06	1	0
Cefepime	≤0.06–8	≤0.06	0.5	0
Amoxicillin-clavulanate	2–64	4	16	11.1
Piperacillin-tazobactam	1–128	2	8	3.7
Gentamicin	0.125–64	0.25	4	5.6
<i>A. baumannii</i> (64)				
Tigecycline	≤0.06–16	2	8	—
Imipenem	0.25–>256	1	128	28.1
Cefepime	2–>256	16	128	37.5
Piperacillin-tazobactam	≤0.06–>256	32	>256	39.1
Ampicillin-sulbactam	2–256	16	64	42.2
Sulbactam	1–64	4	16	—
Levofloxacin	≤0.06–>256	8	32	57.8
Gentamicin	0.25–>256	128	>256	57.8
Polymyxin B	0.25–1	1	1	—
<i>S. maltophilia</i> (52)				
Tigecycline	0.25–8	1	4	—
Trimethoprim-sulfamethoxazole	≤0.06–4	0.125	0.5	1.9
Ticarcillin-clavulanate	1–64	8	64	0
Piperacillin-tazobactam	16–>256	256	>256	67.3
Ceftazidime	2–>256	64	256	73.1
Amikacin	4–>256	64	256	65.4
Trovafoxacin	0.125–8	0.5	4	—
<i>P. aeruginosa</i> (60)				
Tigecycline	4–32	8	16	—
Ceftazidime	0.5–64	2	32	11.7
Cefepime	0.5–16	2	8	0
Imipenem	0.25–16	1	8	6.7
Piperacillin-tazobactam	0.5–>256	4	128	11.7
Gentamicin	0.25–256	2	8	5
Amikacin	2–>256	8	32	1.7
Levofloxacin	0.125–>256	0.5	16	26.7

^a MICs from NCCLS for resistant isolates are as follows: ciprofloxacin, ≥ 4 $\mu\text{g/ml}$; levofloxacin, ≥ 8 $\mu\text{g/ml}$; imipenem and gentamicin, ≥ 16 $\mu\text{g/ml}$; amikacin and cefotaxime, ≥ 64 $\mu\text{g/ml}$; ampicillin-sulbactam and amoxicillin-clavulanate, $\geq 32/16$ $\mu\text{g/ml}$; piperacillin-tazobactam and ticarcillin-clavulanate, $\geq 128/4$ $\mu\text{g/ml}$; —, break-points for tigecycline, sulbactam, polymyxin B, and trovafoxacin are not provided by NCCLS.

^b *E. aerogenes* ($n = 17$) and *E. cloacae* ($n = 33$).

^c *C. freundii* ($n = 37$) and *C. koseri* ($n = 15$).

^d *K. oxytoca* ($n = 22$) and *K. pneumoniae* ($n = 32$).

traditionally used antibiotics and some of the newer β -lactam agents has increasingly been reported (1, 2, 11). Resistance to imipenem was not found, although such resistance has been detected in other Spanish studies (2, 18), but with a low incidence. The new agent tested inhibited 86.7% of all strains at 4 $\mu\text{g/ml}$, and its activity did not vary among the different species of the group. The MIC₅₀s and MIC₉₀s of tigecycline for *B. fragilis* were 1 dilution lower than those recently reported by Gales and Jones (6) but higher than those reported by Edlund and Nord (5). Among toxigenic *Clostridium difficile* isolates, tigecycline showed the lowest MIC₅₀s and MIC₉₀s of all the

antibiotics evaluated. It inhibited 92.7% of strains at 0.125 $\mu\text{g/ml}$. Similar results have been reported previously (5, 6, 20).

In the last two decades, the incidence of infections due to multidrug-resistant gram-positive cocci, such as methicillin-resistant *S. aureus*, vancomycin-resistant enterococci, or penicillin-resistant *S. pneumoniae*, has been on the increase in many parts of the world. Therefore, gram-negative bacilli such as *A. baumannii* and *S. maltophilia*, in which multidrug resistance is common, have emerged as important nosocomial pathogens. These occurrences pose a serious therapeutic challenge and underscore the need for new agents for the treatment of in-

TABLE 3. In vitro activities of tigecycline and other antimicrobial agents against anaerobes

Organism (no. of isolates) and agent	MIC (μg/ml)			% Resistant strains ^a
	Range	50%	90%	
<i>Bacteroides fragilis</i> group (120)				
Tigecycline	≤0.06–8	1	8	—
Cefoxitin	1–128	8	32	7.5
Imipenem	≤0.06–4	0.25	2	0
Amoxicillin-clavulanate	0.125–32	2	16	11.7
Piperacillin-tazobactam	0.25–32	2	16	0
Clindamycin	≤0.06–>256	1	>256	26.7
Metronidazole	≤0.06–4	1	2	0
Moxifloxacin	≤0.06–64	0.25	8	—
<i>B. fragilis</i> (93)				
Tigecycline	≤0.06–8	1	8	—
Cefoxitin	2–128	8	16	4.3
Imipenem	≤0.06–4	0.5	2	0
Amoxicillin-clavulanate	0.125–32	2	8	8.6
Piperacillin-tazobactam	0.25–32	1	4	0
Clindamycin	0.125–>256	1	>256	28.4
Metronidazole	≤0.06–2	1	2	0
Moxifloxacin	≤0.06–64	0.25	8	—
Other <i>B. fragilis</i> group species ^b (27)				
Tigecycline	≤0.06–8	1	4	—
Cefoxitin	1–256	16	64	18.5
Imipenem	≤0.06–4	2	4	0
Amoxicillin-clavulanate	0.125–32	2	16	22.2
Piperacillin-tazobactam	0.25–32	16	32	0
Clindamycin	≤0.06–>256	2	>256	48.1
Metronidazole	0.5–4	1	2	0
Moxifloxacin	0.25–32	2	8	—
<i>C. difficile</i> (55)				
Tigecycline	≤0.06–2	≤0.06	0.125	—
Cefoxitin	64–>256	256	>256	100
Imipenem	≤0.06–64	8	16	45.5
Piperacillin-tazobactam	0.125–16	8	16	0
Metronidazole	≤0.06–1	0.5	1	0
Quinupristin-dalfopristin	≤0.06–32	4	16	—
Linezolid	0.125–16	2	8	—
Moxifloxacin	≤0.06–32	16	16	—

^a MICs from NCCLS for resistant isolates are as follows: metronidazole, ≥ 32 $\mu\text{g/ml}$; clindamycin, ≥ 8 $\mu\text{g/ml}$; cefoxitin, ≥ 64 $\mu\text{g/ml}$; imipenem, ≥ 16 $\mu\text{g/ml}$; amoxicillin-clavulanate, $\geq 16/8$ $\mu\text{g/ml}$; and piperacillin-tazobactam, $\geq 128/4$ $\mu\text{g/ml}$. —, breakpoints for tigecycline, moxifloxacin, quinupristin-dalfopristin, and linezolid are not provided by NCCLS for anaerobes.

^b *B. caccae* ($n = 17$), *B. distasonis* ($n = 1$), *B. merdae* ($n = 2$), *B. ovatus* ($n = 1$), *B. thetaiotaomicron* ($n = 10$), *B. uniformis* ($n = 6$), and *B. vulgatus* ($n = 4$).

fections caused by multidrug-resistant gram-positive and gram-negative pathogens. The results of this study indicate that tigecycline is active against a wide variety of bacterial species including most gram-positive and gram-negative aerobic and anaerobic organisms. This new antibiotic is a promising agent which may have an important role in the therapy of infections caused by antibiotic-resistant gram-positive and gram-negative bacteria.

This study was supported by a financial grant from Wyeth-Ayerst Research, Pearl River, N.Y.

APPENDIX

Members of the Spanish Group of Tigecycline (coordinator, Juan J. Picazo, Madrid) are as follows: J. Aznar (Seville), E. Bouza (Madrid), R. Cisterna (Bilbao), J. García de Lomas (Valencia), J. B. García Moya (Zaragoza), J. A. García-Rodríguez (Salamanca), A. Guerrero

(La Coruña), M. T. Jiménez de Anta (Barcelona), E. J. Perea (Seville), M. de la Rosa (Granada), and J. Ruiz (Murcia).

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