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Telavancin for Hospital-Acquired Pneumonia: Clinical Response and 28-Day Survival

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U.S. Food and Drug Administration draft guidance for future antibiotic clinical trials of bacterial nosocomial pneumonia recommends the use of diagnostic criteria according to American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines and the use of a primary endpoint of 28-day all-cause mortality. The effect of applying these guidelines on outcomes of phase III nosocomial pneumonia studies of telavancin was evaluated in a *post hoc* analysis. ATS/IDSA criteria were applied in a blind fashion to the original all-treated (AT) group. Clinical cure rates at final follow-up were determined in the refined AT and clinically evaluable (CE) groups (ATS/IDSA-AT and ATS/IDSA-CE, respectively). The exploratory endpoint of 28-day survival was evaluated for the ATS/IDSA-AT group. Noninferiority of telavancin versus vancomycin was demonstrated, with similar cure rates in the ATS/IDSA-AT (59% versus 59%) and ATS/IDSA-CE (83% versus 80%) groups. Cure rates favored telavancin in ATS/IDSA-CE patients where *Staphylococcus aureus* was the sole pathogen (86% versus 75%). Overall, 28-day survival rates were similar in the telavancin (76%) and vancomycin (77%) groups but lower in telavancin-treated patients with preexisting moderate-to-severe renal impairment (creatinine clearance [CL_{CR}] of <50 ml/min). Telavancin should be administered to patients with moderate-to-severe renal impairment only if treatment benefit outweighs the risk or if no suitable alternatives are available.

Hospital-acquired pneumonia (HAP) is the second most common nosocomial infection in the United States and is a leading cause of mortality among hospital-acquired infections (1). The rate of HAP is thought to be between 5 and 10 cases per 1,000 admissions in the United States, with the incidence of ventilator-associated pneumonia (VAP) being much higher (1). Data for HAP in Europe are limited, but rates have been estimated to be approximately 3 cases per 1,000 admissions (2). The mortality rate for HAP is high, reaching >50% for VAP in some settings (3). Underlying severe renal impairment has been associated with an excess risk of hospital mortality. In a study of 471 patients admitted to a medical intensive care unit (ICU), acute renal failure was shown by multivariate logistic regression analyses to be an independent predictor of mortality (adjusted odds ratio, 3.7; 95% confidence interval [CI], 2.2 to 6.1) (4). In a much larger study of >17,000 patients admitted to an ICU and requiring renal replacement therapy for acute renal failure, the mortality rate was increased 4-fold (5).

In recent years, there has been a substantial increase in the number cases of pneumonia attributable to multidrug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), which accounts for between 20 and 40% of all HAP and VAP cases (6). Shortcomings associated with the limited number of currently approved treatments for MRSA pneumonia support the need for new treatment options (7).

Telavancin is a lipoglycopeptide antibacterial agent with a dual mechanism of action that combines inhibition of cell wall synthesis and disruption of bacterial cell membrane function (8). Telavancin has demonstrated *in vitro* bactericidal activity against a range of clinically important Gram-positive bacteria, including MRSA (9, 10). Telavancin is approved in the United States and Canada for treatment of adult patients with complicated skin and skin structure infections caused by susceptible Gram-positive pathogens, in the United States for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia due to *S. aureus* (methicillin-susceptible and -resistant isolates) when other alternatives are unsuitable, and in Europe for treatment of MRSA nosocomial pneumonia when other alternatives are unsuitable. (At the time of submission, the telavancin European marketing authorization for the treatment of nosocomial pneumonia was suspended pending evidence of a new European Medicines Agency-approved supplier. Clinigen Healthcare Ltd., Theravance's commercialization partner for telavancin in Europe, is in the process of seeking approval of a new manufacturing source.)

In two methodologically identical, randomized ATTAIN (Assessment of Telavancin for Treatment of Hospital-Acquired Pneumonia) studies, telavancin was shown to be noninferior to vancomycin for treatment of patients with HAP due to Gram-positive pathogens (11). Telavancin cure rates were higher than those of vancomycin in clinically evaluable patients with *S. aureus* as the sole baseline pathogen isolated and in patients infected with *S. aureus* with vancomycin MICs of ≥1 μg/ml (11). Safety findings were comparable for the two treatment groups, while on-study mortality rates were <2% higher in the telavancin group

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TABLE 1 Analysis groups[c]

Analysis	Analysis group	No. (%) of patients					
		Study 0015		Study 0019		Total	
		Telavancin	Vancomycin	Telavancin	Vancomycin	Telavancin	Vancomycin
Original	Original data set, AT	372 (100)	374 (100)	377 (100)	380 (100)	749 (100)	754 (100)
Clinical response and 28-day survival	ATS/IDSA-AT[a]	309 (83)	316 (84)	325 (86)	339 (89)	634 (85)	655 (87)
Clinical response	ATS/IDSA-CE[b]	116 (38)	148 (47)	147 (45)	149 (44)	263 (41)	297 (45)
Clinical response	ATS/IDSA-AT-GP[b]	157 (51)	155 (49)	194 (60)	188 (55)	351 (55)	343 (52)
Clinical response	ATS/IDSA-AT-GPO[b]	115 (37)	113 (36)	110 (34)	111 (33)	225 (35)	224 (34)

[a] Percentages are relative to the AT group.

[b] Percentages are relative to the ATS/IDSA-AT group.

[c] AT, all treated; ATS, American Thoracic Society; CE, clinically evaluable; CL_{CR}, creatinine clearance; GP, Gram positive; GPO, Gram positive only; IDSA, Infectious Diseases Society of America.

than in the vancomycin group, although this difference was not statistically significant (11).

Draft U.S. Food and Drug Administration (FDA) guidance published in 2010 (12) proposed that the inclusion criteria for new clinical studies of treatments for bacterial HAP be modified to include specific diagnostic criteria based on management guidelines developed by the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) (1). The ATS/IDSA guidelines suggest that HAP should be suspected if a patient has the presence of a new or progressive radiographic infiltrate together with clinical findings suggesting infection, which include new onset of fever, purulent sputum, and leukocytosis/leukopenia (1). In addition to recommending the adoption of specific inclusion criteria based on ATS/IDSA guidelines, the draft FDA guidance proposed a primary endpoint of 28-day all-cause mortality, rather than clinical cure, for trials of treatments for HAP (12).

To evaluate the effect of applying the ATS/IDSA diagnostic criteria, the revised inclusion criteria from the draft FDA guidance, and the proposed 28-day all-cause mortality endpoint on the ATTAIN study findings, a *post hoc* analysis was performed, exploring clinical response and 28-day survival endpoints.

(Most of these analyses were presented at the FDA Anti-Infective Drugs Advisory Committee on 28 November 2012 in support of the evaluation of the safety and efficacy of telavancin for the treatment of hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia due to Gram-positive pathogens.)

MATERIALS AND METHODS

This was a *post hoc* analysis of data from two identical, randomized, double-blind, comparator-controlled, parallel-group, phase III ATTAIN clinical trials (study 0015, [NCT00107952] and study 0019 [NCT00124020]), based on supplemental mortality data obtained after study completion. After FDA affirmation that mortality was viewed as an important efficacy variable, the sponsor sought additional patient follow-up to day 28 post-randomization to support a day 28 landmark survival endpoint. This supplemental poststudy mortality status follow-up was successful in obtaining complete 28-day follow-up for approximately 95% of all patients. The remaining 5% were censored at the point of last follow-up prior to day 28.

Details of the study design, methods, and results have been reported previously (11), without the supplemental mortality data or the description of the ATS/IDSA population. In brief, male and nonpregnant female patients aged ≥18 years were eligible for enrollment if they had pneumonia acquired after 48 h in an inpatient acute- or chronic-care facility or that developed within 7 days of discharge. This included hospitalized patients with VAP who developed pneumonia *de novo* after at least 48 h of mechanical ventilation. Eligible patients were randomized 1:1 to receive either 10 mg of telavancin/kg of body weight intravenously every 24 h or 1 g of vancomycin intravenously every 12 h for 7 to 21 days. The vancomycin dosage could be modified per site-specific procedures for body weight and/or renal function as well as vancomycin trough level monitoring, as long as the study blind was maintained.

Patients were assessed at baseline and daily throughout study treatment, at the end of therapy, and at the follow-up/test-of-cure (FU/TOC) visit. FU/TOC assessment was performed 7 to 14 days following the end of therapy. The prespecified primary endpoint was clinical response at the FU/TOC visit, defined as follows. Cure was defined as an improvement or lack of progression of baseline radiographic findings at the end of therapy (EOT) and resolution of signs and symptoms of pneumonia at FU/TOC. Failure was defined as persistence or progression of signs and symptoms or progression of radiological signs of pneumonia at EOT, termination of study medications due to "lack of efficacy" and initiation within 2 calendar days of a different potentially effective antibiotic, death on or after day 3 attributable to primary infection, or relapsed infection at the TOC visit after termination of study medications. An indeterminate response was defined as the inability to determine outcome.

The study protocol for the ATTAIN studies was approved by the institutional review board at each site, and the studies were conducted in accordance with the Declaration of Helsinki. All patients, or their authorized representatives, provided written informed consent.

Analysis populations. The all-treated (AT) population from the two ATTAIN studies comprised all patients who received at least one dose of randomized treatment (11). The ATS/IDSA criteria (presence of new or progressive radiographic infiltration plus two of the following clinical features: fever of >38°C, white blood cell count of >10,000 or <4,500/mm^3, and purulent secretions [1]) were applied in a blind, programmatic fashion to the AT group from the ATTAIN studies to derive the refined all-treated population (ATS/IDSA-AT group). Additional analysis populations were the clinically evaluable (CE) (per-protocol) subgroup of the ATS/IDSA-AT group (ATS/IDSA-CE group), the ATS/IDSA-AT-GP group (patients in the ATS/IDSA-AT group with at least one Gram-positive baseline respiratory pathogen isolated), and the ATS/IDSA-AT-GPO group (patients in the ATS/IDSA-AT group with only Gram-positive baseline pathogens isolated, excluding patients with mixed Gram-positive/Gram-negative infections). The latter two groups are of scientific and regulatory interest because the outcome addresses efficacy in patients with targeted telavancin-susceptible organisms.

Statistical analysis. The primary objective of this *post hoc* analysis was to assess the clinical response at the FU/TOC visit in patients who met the ATS/IDSA diagnostic criteria. Differences in cure rates between the telavancin and vancomycin treatment groups were calculated, together with two-sided 95% CIs. Consistent with the original statistical analysis plan, aggregated analyses of the ATTAIN trials were performed on the basis that these two studies had identical protocol designs and were conducted in approximately the same time frame. Evaluation of clinical response in the

TABLE 2 Baseline characteristics of the ATS/IDSA-AT group[a]

Parameter	Study 0015		Study 0019		Total	
	Telavancin (n = 309)	Vancomycin (n = 316)	Telavancin (n = 325)	Vancomycin (n = 339)	Telavancin (n = 634)	Vancomycin (n = 655)
Mean age (yr) ± SD	62 ± 19.1	64 ± 17.1	60 ± 17.8	61 ± 18.1	61 ± 18.4	62 ± 17.7
No. (%) of patients aged ≥65 yr	160 (52)	176 (56)	159 (49)	167 (49)	319 (50)	343 (52)
No. (%) of female patients	107 (35)	139 (44)	101 (31)	115 (34)	208 (33)	254 (39)
No. (%) of patients of race						
White	222 (72)	232 (73)	209 (64)	224 (66)	431 (68)	456 (70)
African American	8 (3)	10 (3)	13 (4)	5 (1)	21 (3)	15 (2)
Asian	75 (24)	73 (23)	72 (22)	83 (24)	147 (23)	156 (24)
Other	4 (1)	1 (<1)	31 (10)	27 (8)	35 (6)	28 (4)
No. (%) of patients with medical history/comorbidity						
Diabetes	92 (30)	92 (29)	73 (22)	61 (18)	165 (26)	153 (23)
Congestive heart failure	48 (16)	66 (21)	49 (15)	53 (16)	97 (15)	119 (18)
COPD	63 (20)	76 (24)	66 (20)	70 (21)	129 (20)	146 (22)
Chronic renal failure	29 (9)	30 (9)	8 (2)	13 (4)	37 (6)	43 (7)
Shock	13 (4)	22 (7)	13 (4)	14 (4)	26 (4)	36 (5)
ARDS	21 (7)	18 (6)	8 (2)	10 (3)	29 (5)	28 (4)
Acute lung injury	26 (8)	18 (6)	15 (5)	11 (3)	41 (6)	29 (4)
ICU admission	188 (61)	191 (60)	177 (54)	198 (58)	365 (58)	389 (59)
No. (%) of patients with baseline renal status						
Acute renal failure	38 (12)	30 (9)	26 (8)	28 (8)	64 (10)	58 (9)
CL_{CR} ≤ 50 ml/min	117 (38)	124 (39)	91 (28)	91 (27)	208 (33)	215 (33)
Hemodialysis	9 (3)	8 (3)	3 (<1)	5 (1)	12 (2)	13 (2)
No. (%) of patients with use of vasopressor/inotropics[b]	26 (8)	41 (13)	20 (6)	41 (12)	46 (7)	82 (13)
Mean APACHE II score ± SD[c]	16 ± 6.6	16 ± 6.4	15 ± 6.3	16 ± 6.7	15 ± 6.5	16 ± 6.6
No. (%) of patients with pneumonia type						
VAP	94 (30)	88 (28)	103 (32)	103 (30)	197 (31)	191 (29)
Late VAP (≥4 days on ventilation at diagnosis)	83 (27)	71 (22)	91 (28)	83 (24)	174 (27)	154 (24)
No. (%) of patients with sign of pneumonia						
Fever (temp > 38°C)	249 (81)	242 (77)	280 (86)	290 (86)	529 (83)	532 (81)
WBC count of >10,000 cells/mm[c,d]	210 (75)	191 (73)	188 (68)	202 (69)	398 (71)	393 (71)
Purulent secretions	295 (95)	303 (96)	312 (96)	335 (99)	607 (96)	638 (97)
Heart rate of >120 beats/min	68 (22)	63 (20)	56 (17)	59 (17)	124 (20)	122 (19)
Respiratory rate of >30 breaths/min	117 (38)	118 (37)	83 (26)	97 (29)	200 (32)	215 (33)
SIRS[e]	280 (91)	281 (89)	284 (87)	301 (89)	564 (89)	582 (89)
No. (%) of patients with radiological characteristic						
Multilobar involvement	197 (64)	191 (60)	206 (63)	207 (61)	403 (64)	398 (61)
Pleural effusion	96 (31)	105 (33)	86 (26)	96 (28)	182 (29)	201 (31)
No. (%) of patients with prior antibiotic use (>24 h prior to enrollment)						
Any prior antibiotic use	151 (49)	179 (57)	179 (55)	195 (58)	330 (52)	374 (57)
Resistant to prior therapy[f]	26 (17)	36 (20)	45 (25)	51 (26)	71 (22)	87 (23)
Clinical failure of prior therapy[f]	74 (49)	70 (39)	109 (61)	111 (57)	183 (55)	181 (48)
Pneumonia despite prior therapy[f]	77 (51)	93 (52)	86 (48)	88 (45)	163 (49)	181 (48)

[a] AT, all treated; ARDS, acute respiratory disease syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation II; ATS, American Thoracic Society; CL_{CR}, creatinine clearance; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; VAP, ventilator-associated pneumonia; WBC, white blood cell.

[b] Use of dopamine, norepinephrine, dobutamine, epinephrine, or phenylephrine.

[c] Components with missing values were converted to 0.

[d] Denominator includes only patients with a baseline result.

[e] For systemic inflammatory response syndrome (SIRS), patients presented with two or more of the following: temperature of >38°C or <36°C, heart rate of >90 beats/min, respiration rate of >20 breaths/min or $PaCO_2$ value of <32 mmHg, and leukocyte count of >12,000 mm^3, <4,000 mm^3, or 10% immature (band) cells.

[f] Denominator based on the number of patients who used antibiotics >24 h prior.

current analysis was done according to the protocol's prespecified noninferiority margin for a difference in clinical response (telavancin-vancomycin) of −20%, as used in the previously successful HAP trials that led to registration (13).

A secondary objective of this analysis was to assess between-group differences in survival at 28 days in the ATS/IDSA-AT population. Treatment-specific estimates of overall 28-day survival were based on Kaplan-Meier curves. Differences between treatments and corresponding two-sided 95% CIs at day 28 were calculated.

Given the previously noted increased risk of death in critically ill patients in association with severe renal impairment and the reduced efficacy seen with telavancin in patients with preexisting moderate or severe

TABLE 3 Respiratory pathogens isolated at baseline from patients in the ATS/IDSA-AT group who had a baseline pathogen identified[a]

Pathogen	No. (%) of patients					
	Study 0015		Study 0019		Total	
	Telavancin ($n = 217$)	Vancomycin ($n = 212$)	Telavancin ($n = 263$)	Vancomycin ($n = 259$)	Telavancin ($n = 480$)	Vancomycin ($n = 471$)
Respiratory tract pathogen	209 (96)	210 (99)	259 (98)	257 (99)	468 (98)	467 (99)
Isolated from respiratory tract only	191 (88)	194 (92)	246 (94)	236 (91)	437 (91)	430 (91)
Isolated from both respiratory tract and blood	18 (8)	16 (8)	13 (5)	21 (8)	31 (6)	37 (8)
Gram-positive pathogens	151 (70)	153 (72)	191 (73)	187 (72)	342 (71)	340 (72)
Staphylococcus aureus	141 (65)	145 (68)	173 (66)	163 (63)	314 (65)	308 (65)
MRSA	93 (43)	98 (46)	98 (37)	105 (41)	191 (40)	203 (43)
MSSA	52 (24)	47 (22)	76 (29)	60 (23)	128 (27)	107 (23)
Streptococcus pneumoniae	12 (6)	7 (3)	13 (5)	21 (8)	25 (5)	28 (6)
Gram-negative pathogens[b]	100 (46)	98 (46)	152 (58)	147 (57)	252 (53)	245 (52)
Pseudomonas aeruginosa	36 (17)	31 (15)	61 (23)	54 (21)	97 (20)	85 (18)
Acinetobacter calcoaceticus	14 (6)	17 (8)	38 (14)	32 (12)	52 (11)	49 (10)
Klebsiella pneumoniae	11 (5)	18 (8)	23 (9)	32 (12)	34 (7)	50 (11)
Escherichia coli	16 (7)	7 (3)	17 (6)	11 (4)	33 (7)	18 (4)
Stenotrophomonas maltophilia	8 (4)	7 (3)	17 (6)	6 (2)	25 (5)	13 (3)
Pathogen isolated from blood only	26 (12)	18 (8)	17 (6)	23 (9)	43 (9)	41 (9)
Gram positive	22 (10)	14 (7)	12 (5)	17 (7)	34 (7)	31 (7)
Gram negative	5 (2)	5 (2)	6 (2)	7 (3)	11 (2)	12 (3)

[a] More than one pathogen may be present in any patient. AT, all treated; ATS, American Thoracic Society; IDSA, Infectious Diseases Society of America; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*.
[b] Recovered from at least 5% of either treatment group across both studies.

renal impairment and complicated skin and skin structure infections, the survival results, as well as clinical cure results, were stratified by degree of renal impairment (moderate, with a creatinine clearance [CL_{CR}] value of 30 to <50 ml/min, or severe, with a CL_{CR} value of <30 ml/min). Creatinine clearance was estimated by using the Cockcroft-Gault equation. No multiplicity adjustments were made for the multiple statistical comparisons reported here.

The enrolled patients in the combined ATS/IDSA-AT group provided statistical power of 99% (study 0015, 88%; study 0019, 90%) to demonstrate noninferiority of telavancin relative to vancomycin for 28-day survival, with a noninferiority margin of −10%.

RESULTS

Analysis population. The ATS/IDSA-AT group comprised 86% of the original ATTAIN AT group (1,289/1,503) (Table 1). Approximately 13% of the original ATTAIN AT telavancin group and 11% of the vancomycin group had chest X-ray findings and only one clinical feature (primarily purulent sputum); <2% of patients in each group had only chest X-ray changes.

The baseline demographics and characteristics of the ATS/IDSA-AT group are shown in Table 2. Frequencies of baseline comorbidities such as diabetes mellitus, chronic obstructive pulmonary disease, and acute/chronic renal failure were similar between the study and treatment groups. The one notable difference was that the frequency of vasopressor use at baseline in the vancomycin group was almost twice as high as that in the telavancin group in both populations (13% versus 7%). Baseline demographics and characteristics were similar to those of the overall ATTAIN AT population.

The majority of baseline bacterial isolates (91%) were obtained from respiratory specimens only. The remaining isolates were re-

TABLE 4 Clinical response at test of cure in the ATS/IDSA-AT and ATS/IDSA-CE groups (aggregated analysis stratified by study)[a]

Study	Treatment	ATS/IDSA-AT		ATS/IDSA-CE	
		No. of cured patients/ total no. of patients (%)	% difference in telavancin-vancomycin cure rates (95% confidence interval)	No. of cured patients/ total no. of patients (%)	% difference in telavancin-vancomycin cure rates (95% confidence interval)
0015	Telavancin	182/309 (59)	1 (−7.1, 8.4)	99/116 (85)	6 (−2.9, 15.5)
	Vancomycin	184/316 (58)		117/148 (79)	
0019	Telavancin	194/325 (60)	<1 (−7.4, 7.6)	119/147 (81)	>−1 (−9.2, 8.7)
	Vancomycin	202/339 (60)		121/149 (81)	
Total	Telavancin	376/634 (59)	<1 (−5.0, 5.8)	218/263 (83)	3 (−3.6, 9.2)
	Vancomycin	386/655 (59)		238/297 (80)	

[a] AT, all treated; ATS, American Thoracic Society; CE, clinically evaluable; IDSA, Infectious Diseases Society of America.

covered from respiratory and blood cultures or blood cultures only. The most common respiratory tract pathogen isolated at baseline was *S. aureus*, and the majority of the *S. aureus* isolates were MRSA (Table 3). Mixed Gram-positive/Gram-negative infections were identified in 26% (244/951) of ATS/IDSA-AT patients who had a baseline pathogen identified.

Efficacy. For the primary efficacy analysis endpoint of clinical response at FU/TOC visit, noninferiority was supported in both the ATS/IDSA-AT and ATS/IDSA-CE analysis groups for studies 0015 and 0019 separately and when the studies were pooled, with the lower limit of the 95% CIs for all treatment group differences exceeding the prespecified −20% margin and also above −10% (Table 4). Cure rates were 59% (376/634) and 59% (386/655) for telavancin and vancomycin, respectively, in the ATS/IDSA-AT group and 83% (218/263) and 80% (238/297), respectively, in the ATS/IDSA-CE group (both studies combined) (Table 4).

In patients with only *S. aureus* isolated at baseline, cure rates observed for telavancin were higher than those observed for vancomycin in the ATS/IDSA-CE group (86% versus 75%; 95% CI for the difference, 1.2% to 20.8%). The higher cure rates for telavancin were consistent in patients with MRSA, methicillin-susceptible *S. aureus* (MSSA), or *S. aureus* strains with MICs of vancomycin of ≥1 μg/ml, although these differences were not statistically significant owing to smaller sample sizes (Table 5). Cure rates were lower (although not statistically significantly so) in patients with mixed infections (Gram-positive and Gram-negative pathogens) in the telavancin group.

When the clinical cure rate was assessed according to baseline CL_{CR}, numerically lower cure rates with telavancin were observed in patients with baseline CL_{CR} values of <50 ml/min. Of note, regardless of renal function, cure rates in the telavancin group were higher in patients with only Gram-positive pathogens isolated at baseline than in the overall AT population (Table 6).

Analysis of survival at 28 days. The analysis of survival at 28 days revealed similar survival rates between the two treatment groups across the two studies (Fig. 1). Lower survival rates (Kaplan-Meier estimates) were observed for patients treated with telavancin than for patients treated with vancomycin who had moderate-to-severe (CL_{CR}, <50 ml/min) (59% and 70%, respectively) or severe (CL_{CR}, <30 ml/min) (47% and 61%, respectively) renal insufficiency (Fig. 2). For patients with CL_{CR} values of ≥50 ml/min, the survival rate at 28 days for the telavancin group was similar to that for the vancomycin group (84% and 81%, respectively).

Safety. The overall safety findings of the ATTAIN trials were described in detail previously (11). In the ATS/IDSA-AT population, 82% (519/636) of the telavancin group and 81% (532/653) of the vancomycin group experienced at least one adverse event (AE), and 30% (193/636) of the telavancin group and 27% (176/653) of the vancomycin group experienced a serious AE. Discontinuations due to AEs were reported for 8% (51/636) of telavancin-treated patients and 5% (34/653) of vancomycin-treated patients. The incidences of individual AEs were similar in the two treatment groups, with diarrhea, anemia, hypokalemia, and constipation being the most common (>5%) in both treatment groups. Renal AEs (failure, impairment, insufficiency, or elevations in serum creatinine levels) occurred in 9% (59/636) and 8% (51/653) of telavancin- and vancomycin-treated patients, respectively. Among patients with normal baseline renal function, potentially clinically significant increases in serum creatinine levels

TABLE 5 Clinical response by pathogen at test of cure in the ATS/IDSA-CE group (aggregated analysis not stratified by study)[c]

Treatment	*Staphylococcus aureus*[a]		MRSA[a]		MSSA[a]		*Staphylococcus aureus* with vancomycin MIC ≥ 1 μg/ml[a]		*Streptococcus pneumoniae*[a]		Mixed infection (Gram positive + Gram negative)	
	No. of cured patients/total no. of patients (%)	% difference in telavancin-vancomycin cure rates (95% confidence interval)	No. of cured patients/total no. of patients (%)	% difference in telavancin-vancomycin cure rates (95% confidence interval)	No. of cured patients/total no. of patients (%)	% difference in telavancin-vancomycin cure rates (95% confidence interval)	No. of cured patients/total no. of patients (%)	% difference in telavancin-vancomycin cure rates (95% confidence interval)	No. of cured patients/total no. of patients (%)	% difference in telavancin-vancomycin cure rates (95% confidence interval)	No. of cured patients/total no. of patients (%)	% difference in telavancin-vancomycin cure rates (95% confidence interval)
Telavancin	103/120 (86)	11 (1.2, 20.8)	59/69 (86)	11 (−1.5, 22.5)	44/51 (86)	12 (−5.8, 30.2)[b]	61/69 (88)	12 (−0.4, 22.9)[b]	11/12 (92)	2 (−25.6, 30.3)[b]	37/59 (63)	−15 (−30.5, 1.6)[b]
Vancomycin	95/127 (75)		72/96 (75)		23/31 (74)		69/90 (77)		9/10 (90)		48/61 (79)	

[a] Includes patients with monomicrobial Gram-positive infection; patients with a mixed Gram-positive/Gram-negative infection are not included.
[b] Confidence interval using Agresti-Caffo adjustment.
[c] ATS, American Thoracic Society; CE, clinically evaluable; IDSA, Infectious Diseases Society of America; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*.

TABLE 6 Clinical cure rate by baseline creatinine clearance (aggregated analysis not stratified by study)[a]

CL_{CR} (ml/min)	Treatment	ATS/IDSA-AT		ATS/IDSA-AT-GP		ATS/IDSA-AT-GPO	
		No. of cured patients/total no. of patients (%)	% difference in telavancin-vancomycin cure rates (95% confidence interval)	No. of cured patients/total no. of patients (%)	% difference in telavancin-vancomycin cure rates (95% confidence interval)	No. of cured patients/total no. of patients (%)	% difference in telavancin-vancomycin cure rates (95% confidence interval)
<30	Telavancin	32/83 (39)	−8 (−23.4, 6.6)	15/37 (41)	−11 (−32.4, 11.1)	10/23 (43)	−7 (−33.2, 20.1)
	Vancomycin	39/83 (47)		22/43 (51)		16/32 (50)	
≥30	Telavancin	344/551 (62)	2 (−3.9, 7.5)	189/314 (60)	−1 (−8.5, 6.9)	142/202 (70)	8 (−1.5, 17.1)
	Vancomycin	347/572 (61)		183/300 (61)		120/192 (63)	
<50	Telavancin	92/197 (47)	−8 (−17.5, 1.9)	45/95 (47)	−6 (−19.5, 7.9)	38/68 (56)	2 (−13.8, 18.2)
	Vancomycin	114/209 (55)		59/111 (53)		44/82 (54)	
≥50	Telavancin	284/437 (65)	4 (−2.4, 10.4)	159/256 (62)	−1 (−9.4, 7.8)	114/157 (73)	8 (−2.7, 18.3)
	Vancomycin	272/446 (61)		146/232 (63)		92/142 (65)	

[a] AT, all treated; ATS, American Thoracic Society; CE, clinically evaluable; CL_{CR}, creatinine clearance; GP, Gram positive; GPO, Gram positive only; IDSA, Infectious Diseases Society of America.

(maximum value of ≥1.33 mg/dl and at least a 50% increase from baseline) occurred in 14% (71/505) of the telavancin group and in 10% (50/523) of the vancomycin group.

DISCUSSION

The ATTAIN studies were two methodologically identical, randomized, phase III studies that demonstrated the noninferiority of telavancin relative to vancomycin for the treatment of HAP, including VAP, due to Gram-positive organisms on the basis of clinical response (11). In this *post hoc* analysis, the ATS/IDSA HAP diagnostic criteria were applied to the AT study group from the ATTAIN studies to evaluate the potential effect on clinical outcomes. The results of this analysis support the noninferiority of telavancin relative to vancomycin with regard to clinical response when the ATS/IDSA diagnostic criteria were applied. Furthermore, our analysis suggests that patients with infections due solely to *S. aureus* (MRSA or MSSA) treated with telavancin had higher cure rates than such patients treated with vancomycin. This may be related to a better *in vitro* activity of telavancin against *S. aureus*, including strains with higher vancomycin MICs. Given these findings, it would be appropriate to consider telavancin as a therapeutic option for the management of pneumonia due to *S. aureus* (MRSA and MSSA) in patients without moderately to severely compromised renal function and as potentially useful in patients with compromised renal function if no other suitable alternatives are available.

Antibiotic resistance poses a significant risk to public health. The incidence of MRSA continues to increase (6), while infections due to vancomycin-intermediate *S. aureus*, heteroresistant vancomycin-intermediate *S. aureus*, and vancomycin-resistant *S. aureus*

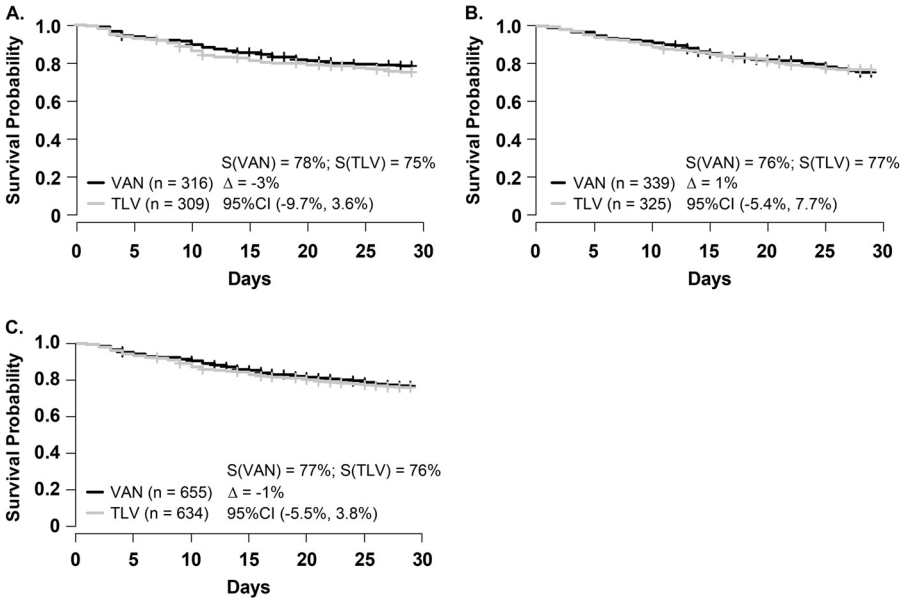

FIG 1 Kaplan-Meier survival curves showing 28-day survival in study 0015 (A), study 0019 (B), and the aggregate (C) for the ATS/IDSA-AT population. CI, confidence interval; S, survival rate; TLV, telavancin; VAN, vancomycin.

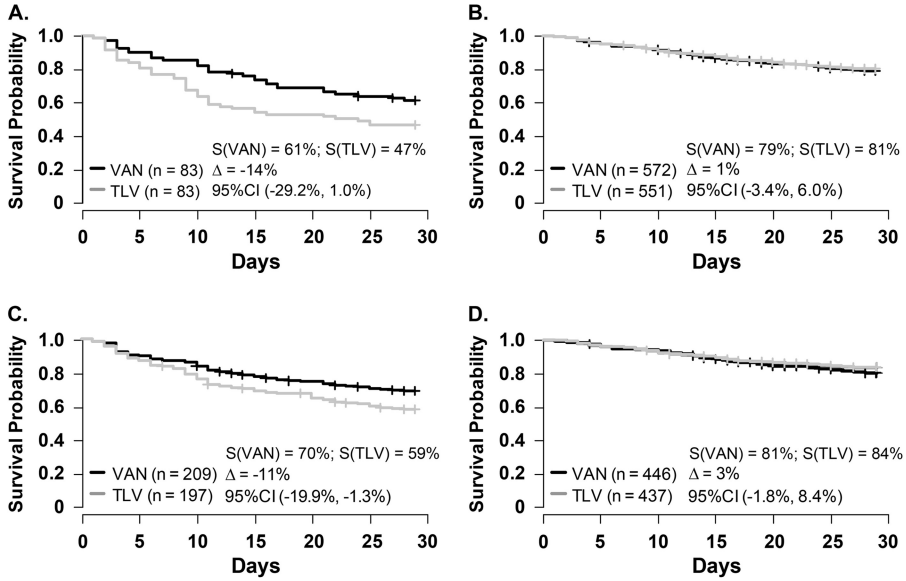

FIG 2 Kaplan-Meier survival curves showing 28-day survival for the ATS/IDSA-AT population (aggregated studies 0015 and 0019) in patients with CL_{CR} values of <30 ml/min (A), ≥30 ml/min (B), <50 ml/min (C), and ≥50 ml/min (D). CI, confidence interval; CL_{CR}, creatinine clearance; S, survival rate; TLV, telavancin; VAN, vancomycin.

have also emerged (14, 15). The previously reported results of the ATTAIN studies suggested that telavancin was potentially more effective than vancomycin in patients infected with *S. aureus* strains with vancomycin MICs of ≥1 μg/ml (11). Although not statistically significant (owing to a smaller sample size of patients), the same trend was observed in this analysis, with a similarly large and clinically meaningful difference in cure rates between the treatment groups. Therefore, telavancin may be a reasonable empirical therapeutic option in centers with high rates of *S. aureus* with elevated vancomycin MICs.

Analysis of 28-day all-cause survival showed similar survival rates between telavancin-treated and vancomycin-treated patients, although our analysis did highlight lower survival rates in patients with moderate or severe renal dysfunction who received telavancin than in those who received vancomycin. The mechanism of this increased risk is unclear, and interpretation of mortality as an endpoint of HAP is confounded by nonattributable mortality, which may be the result of variables that are unrelated to pneumonia. The ATTAIN studies evaluated clinical outcome as the primary endpoint and thus excluded only cases where death was expected within 7 days. However, despite appropriate dosage adjustments for renal function, nephrotoxicity due to telavancin in patients with preexisting renal impairment cannot be ruled out as a contributing factor. The use of telavancin in patients with CL_{CR} values of <50 ml/min should therefore be considered only when the benefits outweigh any potential risks or if other alternatives are not suitable. Monitoring of renal function in these patients should be performed routinely (11).

Limitations of this study include the fact that it is a *post hoc* analysis. The ATS/IDSA criteria were, however, applied programmatically in a blind fashion. Using these criteria, it was possible to ensure that the patients included in the analysis were those most likely to have pneumonia. However, each of the analyses used a subgroup of the original ATTAIN study population, with decreasing numbers of patients in each analysis group potentially reducing the power of the analysis to demonstrate noninferiority. That said, the all-treated group retained a sufficient sample size to ensure adequate statistical power. The 28-day mortality endpoint, while potentially confounded by nonattributable mortality, is an objective outcome measure and, in these studies, identified a group of patients for whom caution should be taken when considering the use of telavancin.

Conclusions. The results of this reanalysis of the ATTAIN patient population suggest that telavancin is noninferior to vancomycin for clinical cure of HAP, including VAP, due Gram-positive organisms when the ATS/IDSA diagnostic criteria are applied. In this analysis, cure rates against *S. aureus* were numerically higher than those with vancomycin for both MRSA and MSSA infections, suggesting that telavancin is an effective therapy for HAP due to *S. aureus*, including cases caused by *S. aureus* strains with high or unknown vancomycin MICs. The use of telavancin in patients with preexisting moderate-to-severe renal function should be considered only if the benefits of treatment outweigh the risks or in the absence of other suitable alternatives.

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AUTHOR CORRECTION

Telavancin for Hospital-Acquired Pneumonia: Clinical Response and 28-Day Survival

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Volume 58, no. 4, p 2030–2037, 2014. Page 2030, right column, line 6. Since the suspension of the European marketing authorization for telavancin has now been lifted, the following text in the introduction no longer applies: "At the time of submission, the telavancin European marketing authorization for the treatment of nosocomial pneumonia was suspended pending evidence of a new European Medicines Agency-approved supplier. Clinigen Healthcare Ltd., Theravance's commercialization partner for telavancin in Europe, is in the process of seeking approval of a new manufacturing source."

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