Pharmacological and Patient-Specific Response Determinants in Patients with Hospital-Acquired Pneumonia Treated with Tigecycline

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Pharmacokinetic and clinical data from tigecycline-treated patients with hospital-acquired pneumonia (HAP) who were enrolled in a phase 3 clinical trial were integrated in order to evaluate pharmacokinetic-pharmacodynamic (PK-PD) relationships for efficacy. Univariable and multivariable analyses were conducted to identify factors associated with clinical and microbiological responses, based on data from 61 evaluable HAP patients who received tigecycline intravenously as a 100-mg loading dose followed by 50 mg every 12 h for a minimum of 7 days and for whom there were adequate clinical, pharmacokinetic, and response data. The final multivariable logistic regression model for clinical response contained albumin and the ratio of the free-drug area under the concentration-time curve from 0 to 24 h ($fAUC_{0-24}$) to the MIC ($fAUC_{0-24}$:MIC ratio). The odds of clinical success were 13.0 times higher for every 1-g/dl increase in albumin ($P < 0.001$) and 8.42 times higher for patients with $fAUC_{0-24}$:MIC ratios of ≥ 0.9 compared to patients with $fAUC_{0-24}$:MIC ratios of < 0.9 ($P = 0.008$). Average model-estimated probabilities of clinical success for the albumin/ $fAUC_{0-24}$:MIC ratio combinations of < 2.6 / < 0.9 , < 2.6 / ≥ 0.9 , ≥ 2.6 / < 0.9 , and ≥ 2.6 / ≥ 0.9 were 0.21, 0.57, 0.64, and 0.93, respectively. For microbiological response, the final model contained albumin and ventilator-associated pneumonia (VAP) status. The odds of microbiological success were 21.0 times higher for every 1-g/dl increase in albumin ($P < 0.001$) and 8.59 times higher for patients without VAP compared to those with VAP ($P = 0.003$). Among the remaining variables evaluated, the MIC had the greatest statistical significance, an observation which was not surprising given the differences in MIC distributions between VAP and non-VAP patients (MIC₅₀ and MIC₉₀ values of 0.5 and 0.25 mg/liter versus 16 and 1 mg/liter for VAP versus non-VAP patients, respectively; $P = 0.006$). These findings demonstrated the impact of pharmacological and patient-specific factors on the clinical and microbiological responses.

The clinical study of new antimicrobial agents, especially those for drug-resistant bacteria, in the treatment of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) remains challenging. Superficially, for the drug developer, program challenges are operational and financial. While operational failures in the conduct of a clinical trial can certainly imperil a development program (6) and the financial burden of conducting large, randomized, multinational programs is great (7), the more fundamental challenge involves heterogeneity. Heterogeneity in patient-, institution-, and intervention-specific factors can make it difficult to discern treatment effects (14, 15).

Recently, three antimicrobial agents, ceftobiprole, doripenem, and tigecycline, either failed to gain U.S. Food and Drug Administration (FDA) approval (5, 6, 18) for the treatment of patients suffering from HAP or VAP or the sponsors opted not to file with the FDA for approval due to suboptimal clinical results. Excluding issues related to proper clinical trial conduct and unexpected toxicities, suboptimal drug exposure in the patient population of interest can lead to regulatory roadblocks, even for drug development programs containing appropriately sized clinical trials (3). The conduct of pharmacokinetic-pharmacodynamic (PK-PD) analyses for determinations of efficacy utilizing clinical data allows for the evaluation of the influence of drug exposure in the context of *in vitro* microbiological activity on response in the entire population and, importantly, in the subpopulations of interest. Moreover, the influence of heterogeneity in patient-specific factors on response (response modifiers) can also be evaluated in the context of drug exposure.

In the analyses described herein, pharmacokinetic and clinical

data from tigecycline-treated patients with HAP enrolled in a phase 3 clinical trial were integrated in order to evaluate PK-PD relationships for efficacy. Patient-specific PK parameter estimates were available from a population PK analysis and were utilized to provide estimates of individual patient tigecycline exposure. These exposure estimates were indexed to the MIC of the infecting pathogen(s) and, along with other patient-specific factors, were evaluated as determinants of response.

MATERIALS AND METHODS

Patient population. Patient data for these analyses were from tigecycline-treated patients enrolled in a randomized, multicenter, double-blind, phase 3 clinical trial comparing the efficacy and safety of tigecycline (with or without ceftazidime and/or an aminoglycoside) with that of imipenem-cilastatin (with or without vancomycin and/or an aminoglycoside) in patients with HAP (9).

Hospitalized patients 18 years of age and older who were known or suspected of having acute HAP were eligible for enrollment. Acute HAP was defined as pneumonia with the onset of symptoms at ≥ 48 h after

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admission to the hospital or ≤ 7 days after discharge from the hospital (duration of previous hospitalization had to be ≥ 3 days).

Clinical criteria for inclusion were (i) presence of a new or evolving infiltrate observed on a chest X-ray film; (ii) fever or leukocytosis; and (iii) in the absence of respiratory failure requiring mechanical ventilation, the presence of at least two of the following: cough, dyspnea or tachypnea, auscultatory findings of rales or pulmonary consolidation, hypoxemia, or purulent sputum production.

Patients were excluded for any of the following reasons: presence of coincident pulmonary conditions (cystic fibrosis, pulmonary malignancy, known bronchial-obstructive or postobstructive pneumonia, pulmonary abscess, empyema, known or suspected active tuberculosis, bronchiectasis, sarcoidosis, or known or suspected pulmonary infection caused by *Pneumocystis jirovecii*, *Legionella* spp., mycobacteria, fungi, parasites, or viruses); concurrent hemodialysis, hemofiltration, peritoneal dialysis, or plasmapheresis; sustained shock at the time of randomization; known hypersensitivity to any of the study drugs; treatment with ganciclovir; brain lesions or central nervous system disease precluding use of imipenem-cilastatin; APACHE II score of >30 ; presence of laboratory abnormalities indicative of neutropenia or hepatic dysfunction, or creatinine clearance of <41 ml/min/1.73 m²; anticipated discharge from the hospital in less than 7 days; known or suspected concomitant bacterial infection requiring additional systemic antibacterial treatment; antibacterial drugs administered for >24 h to treat the current episode of suspected HAP, unless a repeat respiratory culture showed that a pathogen was resistant to that agent and/or the subject had worsening or no improvement for the clinical signs and symptoms of pneumonia (note that a patient may not have failed one of the study medications or an agent of the same class); any investigational drugs taken or investigational devices used within 4 weeks before the first dose of the test article; known human immunodeficiency virus (HIV) infection; immunosuppressive therapy that, in the opinion of the investigator, would decrease the subject's ability to eradicate the infection (including chronic treatment with >10 mg/day of systemic prednisone or equivalent for greater than 3 weeks prior to randomization); life expectancy estimated at <1 month; pregnant women or nursing mothers; female patients of childbearing potential who did not agree to practice sexual abstinence or use a medically acceptable method of contraception throughout the duration of the study and for at least 1 month after the last dose of test article administration; any other major illness/condition that, in the investigator's judgment, would substantially increase the risk associated with the subject's participation in, and completion of, the study or could preclude the evaluation of the subject's response.

Drug dosage and administration. Patients randomized to tigecycline received an intravenous (i.v.) loading dose of 100 mg of tigecycline followed by 50 mg of tigecycline i.v. every 12 h infused over 30 to 60 min for a minimum of 7 days.

Outcome evaluation. Patients were assessed for both clinical and microbiological responses. The clinical response was determined by comparing the patient's baseline signs and symptoms of infection with those after therapy. Success was defined as the resolution or improvement of all signs and symptoms present at study entry by the time of the test-of-cure visit (approximately 10 to 21 days after the end of therapy), improvement or no worsening in chest X-ray, no appearance of new signs and symptoms, and no need for further antibiotics. Failure was defined as the occurrence of any one or more of the following circumstances: a lack of response which required additional intervention and/or additional antibacterial therapy, initial recovery followed by deterioration before the test-of-cure visit, or death after study day 2 due to pneumonia.

Microbiological response was assessed in those patients who were clinically evaluable with one or more susceptible pretreatment pathogens. The microbiological response to therapy at the patient level was classified as either eradicated (which included eradicated or presumed eradicated), persistent (which included persistent or presumed persistent), superinfection, or indeterminate. Eradicated was defined as the absence of the pretreatment pathogen(s) from the posttreatment culture. If the clinical

response was classified as a success and no material was available for culture, the pretreatment pathogen(s) was presumed eradicated. Persistent was defined as the presence of the pretreatment pathogen(s) in the post-treatment culture. If the clinical response was classified as a failure and no material was available for culture, the pretreatment pathogen(s) was presumed persistent. Superinfection was defined as emergence of a new pathogen during therapy, with emergence or worsening of signs and symptoms of infection. Indeterminate was defined as follows: a subject had no outcome determination for reasons unrelated to study drug, no baseline pathogens were identified, or death occurred within 2 days of the first dose of study drug.

For the purposes of the analyses described herein, patients with a microbiological outcome of superinfection were classified as failures, while those classified as indeterminate were excluded (since a baseline pathogen was necessary for calculation of the PK-PD index).

Calculation of PK-PD indices for the AUC_{0-24} and $fAUC_{0-24}$:MIC ratio. Given that preclinical data for tigecycline have demonstrated that the ratio of the area under the concentration-time curve (AUC) to the MIC is the PK-PD index most predictive of efficacy (8), this measure, adjusted for protein binding, was calculated and evaluated as a determinant of response. The steady-state AUC from 0 to 24 h (AUC_{0-24}) for tigecycline was calculated according to the following equation: $AUC_{0-24} = \text{dose}/CL_t$, where dose was the total daily dose of tigecycline (100 mg) and CL_t was the Bayesian *post hoc* clearance value, generated from the fit of a previously described population PK model to the measured tigecycline concentrations for each patient. The population PK model is briefly described below (17). The disposition of tigecycline was best described by a two-compartment model with linear elimination; the primary structural parameters were total clearance (mean, 19.2 liters/h; coefficient of variation [CV], 40.4%), volume of central compartment (mean, 65.2 liters; CV, 82.1%), distributional clearance from the central to the peripheral compartment (mean, 85.1 liters/h; CV, 110%), and volume of distribution at steady state (mean, 398 liters; CV, 40.2%). Significant covariates predicting interindividual variability in total clearance were body surface area and creatinine clearance. This model fit the tigecycline serum concentration data from these patients well. A strong correlation ($r^2 = 0.992$) between observed and model-fitted concentrations was apparent; the slope and intercept for the line of best fit were 1.07 and -0.0157 , respectively. In additional, examination of other relevant diagnostic plots demonstrated no apparent bias in the fit.

The ratio of the free-drug (f) AUC from 0 to 24 h to the MIC ($fAUC_{0-24}$:MIC) was calculated using the following equation: $fAUC_{0-24}$:MIC = $(f_u \times AUC_{0-24})/\text{MIC}$, where f_u is the fraction of unbound tigecycline, which was assumed to be 0.20 (18), and the MIC was the baseline MIC selected as described below.

Baseline culture data were reviewed for each patient in order to identify the MIC to be used in the calculation of the PK-PD index. Those baseline isolates deemed pathogens and considered to be the primary infecting pathogen(s) were considered. In the case of patients with multiple pathogens, the highest MIC value was chosen for the PK-PD index calculation. However, the MIC values for those organisms isolated from blood were given priority consideration over those isolated from sputum, regardless of MIC value. Given the heterogeneous nature of the pathogens associated with VAP and non-VAP, subsets of similar pathogens were identified, and a categorical variable for pathogen group was constructed and considered for evaluation in the univariable and multivariable analyses conducted.

Univariable and multivariable analyses. Univariable and multivariable analyses for efficacy involved the evaluation of two endpoints for efficacy: clinical response (therapeutic success versus failure) and microbiological response (eradicated or presumed eradicated versus persistent or presumed persistent). All analyses were performed using R software version 2.4.1 (16).

The assessment of pharmacologic determinants for each response variable included the assessment of the $fAUC_{0-24}$, MIC, and $fAUC_{0-24}$:

MIC ratio. Univariable associations with response based on these independent variables included the examination of the observed and log-transformed form of each variable and the identification of threshold values distinguishing cohorts of patients with impressive differences in response, in order to construct two- and three-group categorical variables. The latter set of variables was examined to account for potential nonlinearity and nonmonotonicity, respectively. Two-group independent variables were constructed using the resulting split of a classification tree for a given outcome variable. Three-group independent variables were constructed by determining a pair of cutoff values that minimized the likelihood ratio P value for a given outcome variable.

In addition to the above-described pharmacologic-based independent variables, relationships between clinical or microbiological response and additional independent variables assessed at baseline were evaluated. These independent variables included age, albumin, altered mental status, APACHE II score, creatinine clearance (normalized for body surface area), VAP status, pathogen group, and prior nursing home stay. Age, albumin, APACHE II score, and creatinine clearance were evaluated in their observed continuous forms and, like the pharmacological-based variables, as two- and three-group categorical variables relative to each response variable.

All univariable evaluations were conducted using contingency tables (chi-square test or Fischer's exact test, as appropriate) for dichotomous independent variables and logistic regression for continuous independent variables. Multivariable logistic regression analyses were conducted using forward inclusion of independent variables with an entry criterion of a P level of <0.05 to arrive at a final model. Likelihood ratio P values were assessed throughout the forward inclusion process. All independent variables (including the continuous and two- and three-group forms of each variable) were considered for inclusion into the base model. However, once a single form of a given independent variable entered the model, no other forms of the same variable were considered for entry at subsequent steps. The limits placed on the number of independent variables included in a model were based on recommendations from Hosmer and Lemeshow for logistic regression (10). Interactions among resulting independent variables retained in final models were evaluated.

Model-predicted probabilities of a successful response were assessed relative to observed proportions of successful responses for cohorts of patients as described by independent variables included in the final multivariable logistic regression models. In order to describe the observed proportions of a successful response for continuous independent variables, such variables were categorized using the thresholds defining two-group variables (identified using classification trees). Model-predicted probabilities within cohorts were averaged among the patients in each cohort.

RESULTS

Of the 233 clinically and microbiologically evaluable patients, there were sufficient PK data and at least one pathogen isolated at baseline with a corresponding MIC value for a total of 61 patients. The median (minimum [min], maximum [max]) age of the 61 patients was 56 (18, 89) years of age. The median (min, max) APACHE II score was 12 (3, 28). A total of 23 patients had VAP (37.7%). Summary statistics for all demographic and disease-related factors evaluated are provided in Table S1 of the supplemental material.

Among the 61 patients, 29 had monomicrobial infections, while 32 patients had polymicrobial infections. In total, 101 pathogens were isolated from 61 patients. Table S2 of the supplemental material shows the counts of organisms by pathogen group for those organisms for which the MIC was used to calculate the $fAUC_{0-24}$:MIC ratio. The highest percentage of organisms was represented by *Enterobacteriaceae* species (39.3%; 24/61), followed by *Staphylococcus aureus* (21.3%; 13/61) and those that

were either *Acinetobacter* species or *Pseudomonas aeruginosa* (16.4%; 10/61). The MIC_{50} and MIC_{90} values (minimum and maximum) were 0.25 and 2 mg/liter (0.03, 64). The distribution of MIC values, overall and stratified by pathogen group, is provided in Table S3 of the supplemental material.

The median (minimum, maximum) $fAUC_{0-24}$ and $fAUC_{0-24}$:MIC ratio was 1.08 mg/liter $\cdot$ h (0.356, 4.02) and 3.56 (0.006, 54.1). The percentages of clinical and microbiological successes were 70.5% (43/61) and 72.1% (44/61), respectively; the percentage of overall mortality was 8.2% (5/61).

A summary of the results of the evaluation of univariable relationships between the $fAUC_{0-24}$, MIC, and $fAUC_{0-24}$:MIC ratio and clinical and microbiological responses is provided in Table 1. The remainder of results based on the evaluation of other independent variables is provided in Table S1 of the supplemental material. The independent variables that demonstrated the most significant association with both response variables were altered mental status ($P < 0.001$) and albumin ($P \leq 0.002$ for all forms of the variable). When evaluating continuous forms of the pharmacological-based independent variables, the $\log_{10}$ transformation of $fAUC_{0-24}$:MIC ratio was most significantly associated with a clinical ($P = 0.023$) and microbiological ($P = 0.031$) response. However, among all of the forms of this variable evaluated, $fAUC_{0-24}$:MIC ratio as a two-group variable (as determined using classification trees) was most closely associated with clinical ($P = 0.011$) and microbiological ($P = 0.015$) responses. For patients for which $fAUC_{0-24}$:MIC ratios were ≥ 0.9 , 78.0% of patients had a successful clinical response; below this threshold, 36.4% of patients had a successful clinical response. For microbiological response, $fAUC_{0-24}$:MIC ratios of 0.35 were associated with higher response rates; 77.8% of patients with $fAUC_{0-24}$:MIC ratios of ≥ 0.35 had a successful response, while 28.6% of patients with $fAUC_{0-24}$:MIC ratios of <0.35 had a successful response. Figure 1A and B show the estimated logistic regression functions for the univariable relationship between the probabilities of clinical and microbiological success and the $fAUC_{0-24}$:MIC ratio, respectively, with 95% pointwise confidence bounds. In each figure, the estimated logistic regression function overlays the observed $fAUC_{0-24}$:MIC ratio distribution; the solid box on the estimated logistic regression function represents the threshold for the above-described two-group variables for $fAUC_{0-24}$:MIC ratios of 0.9 and 0.35, respectively. Given the concordance between clinical and microbiological responses, the similarities in the estimated functions for each of these response variables were not unexpected.

Increased $fAUC_{0-24}$ and lower MIC values were each associated with a higher probability of clinical and microbiological success. In comparison to the $fAUC_{0-24}$:MIC ratio, the relationships between the $fAUC_{0-24}$ or MIC, regardless of form, and either clinical or microbiological response were generally less significant. Interestingly, such relationships between $fAUC_{0-24}$, MIC, and $fAUC_{0-24}$:MIC ratio, regardless of form, and all-cause mortality were not found ($P \geq 0.20$). Of the remaining independent variables considered, univariable relationships for clinical or microbiological response with either APACHE II score (irrespective of the form of the variable) or VAP status were of similar significance and intuitive; higher APACHE II scores and VAP were associated with a lower probability of successful responses.

Given the univariable findings with VAP status and the potential for both the distribution of $fAUC_{0-24}$ and MIC values to differ between VAP and non-VAP patients due to possible differences in

TABLE 1 Univariable relationships between fAUC₀₋₂₄, MIC, or fAUC₀₋₂₄:MIC ratio and clinical and microbiological responses

Independent variable type and range ^a	% or median (n/N or min, max)			Microbiological response				
	Clinical response			Microbiological response				
	Overall	Success (n = 43)	Failure (n = 18)	P value	Overall	Success (n = 44)	Failure (n = 17)	P value
fAUC ₀₋₂₄ , continuous variable	1.08 (0.356, 4.02)	1.14 (0.410, 4.02)	0.981 (0.356, 3.11)	0.55	1.08 (0.356, 4.02)	1.15 (0.410, 4.02)	0.938 (0.356, 2.62)	0.19
fAUC ₀₋₂₄ , two-group variable	31.1 (19/61)	52.6 (10/19)	47.4 (9/19)	0.044	16.4 (10/61)	40.0 (4/10)	60.0 (6/10)	0.022
<0.95/ ^b ≥0.7 ^b	68.9 (42/61)	78.6 (33/42)	21.4 (9/42)		83.6 (51/61)	78.4 (40/51)	21.6 (11/51)	
fAUC ₀₋₂₄ , three-group variable				0.033				0.06
≤1.2	65.6 (40/61)	65.0 (26/40)	35.0 (14/40)		65.6 (40/61)	65.0 (26/40)	35.0 (14/40)	
>1.2 to ≤1.7	18.0 (11/61)	100 (11/11)	0 (0/11)		18.0 (11/61)	100 (11/11)	0 (0/11)	
>1.7	16.4 (10/61)	60.0 (6/10)	40.0 (4/10)		16.4 (10/61)	70.0 (7/10)	30.0 (3/10)	
Log ₁₀ fAUC ₀₋₂₄ , continuous variable	0.0327 (−0.448, 0.605)	0.0580 (−0.387, 0.605)	−0.00855 (−0.448, 0.493)	0.35	0.0327 (−0.448, 0.605)	0.0599 (−0.387, 0.605)	−0.0276 (−0.448, 0.419)	0.11
Log ₁₀ fAUC ₀₋₂₄ , two-group variable	31.1 (19/61)	52.6 (10/19)	47.4 (9/19)	0.044	16.4 (10/61)	40.0 (4/10)	60.0 (6/10)	0.022
<−0.02/ ^b ≥−0.15 ^b	68.9 (42/61)	78.6 (33/42)	21.4 (9/42)		83.6 (51/61)	78.4 (40/51)	21.6 (11/51)	
Log ₁₀ fAUC ₀₋₂₄ , three-group variable				0.29				0.049
≤0.1/ ^b ≥−0.1 ^b	67.2 (41/61)	65.9 (27/41)	34.1 (14/41)		21.3 (13/61)	46.2 (6/13)	53.8 (7/13)	
>0.1 to ≤0.3/ ^b ≥−0.1 to ≤0.1 ^b	18.0 (11/61)	90.9 (10/11)	9.1 (1/11)		45.9 (28/61)	75.0 (21/28)	25.0 (7/28)	
>0.3/ ^b >0.1 ^b	14.8 (9/61)	66.7 (6/9)	33.3 (3/9)		32.8 (20/61)	85.0 (17/20)	15.0 (3/20)	
MIC, continuous variable	0.25 (0.03, 64)	0.25 (0.03, 32)	0.5 (0.06, 64)	0.17	0.25 (0.03, 64)	0.25 (0.03, 32)	0.5 (0.06, 64)	0.16
MIC, two-group variable	<2	76.0 (38/50)	24.0 (12/50)	0.07	82.0 (50/61)	78.0 (39/50)	22.0 (11/50)	0.06
≥2	18.0 (11/61)	45.5 (5/11)	54.5 (6/11)		18.0 (11/61)	45.5 (5/11)	54.5 (6/11)	
MIC, three-group variable				0.11				0.1
≤0.12/ ^b ≥0.25 ^b	29.5 (18/61)	83.3 (15/18)	16.7 (3/18)		52.5 (32/61)	75.0 (24/32)	25.0 (8/32)	
>0.12 to ≤1/ ^b >0.25 to ≤1 ^b	52.5 (32/61)	71.9 (23/32)	28.1 (9/32)		29.5 (18/61)	83.3 (15/18)	16.7 (3/18)	
>1	18.0 (11/61)	45.5 (5/11)	54.5 (6/11)		18.0 (11/61)	45.5 (5/11)	54.5 (6/11)	
Log ₂ MIC, continuous variable	−2.00 (−5, 6)	−2.00 (−5, 5)	−1.00 (−4, 6)	0.028	−2.00 (−5, 6)	−2.00 (−5, 5)	−1.00 (−4, 6)	0.06
Log ₂ MIC, two-group variable	<1	76.0 (38/50)	24.0 (12/50)	0.07	82.0 (50/61)	78.0 (39/50)	22.0 (11/50)	0.06
≥1	18.0 (11/61)	45.5 (5/11)	54.5 (6/11)		18.0 (11/61)	45.5 (5/11)	54.5 (6/11)	
Log ₂ MIC, three-group variable				0.11				0.1
≤−3/ ^b ≥−2 ^b	29.5 (18/61)	83.3 (15/18)	16.7 (3/18)		52.5 (32/61)	75.0 (24/32)	25.0 (8/32)	
>−3 to ≤0/ ^b ≥−2 to ≤0 ^b	52.5 (32/61)	71.9 (23/32)	28.1 (9/32)		29.5 (18/61)	83.3 (15/18)	16.7 (3/18)	
>0	18.0 (11/61)	45.5 (5/11)	54.5 (6/11)		18.0 (11/61)	45.5 (5/11)	54.5 (6/11)	
fAUC ₀₋₂₄ :MIC ratio, continuous variable	3.56 (0.006, 54.1)	4.40 (0.049, 54.1)	1.69 (0.006, 18.9)	0.13	3.56 (0.006, 54.1)	4.16 (0.049, 54.1)	2.23 (0.0056, 18.9)	0.17
fAUC ₀₋₂₄ :MIC ratio, two-group variable	<0.9/ ^b ≥0.35 ^b	36.4 (4/11)	63.6 (7/11)	0.011	11.5 (7/61)	28.6 (2/7)	71.4 (5/7)	0.015
≥0.9/ ^b ≥0.35 ^b	82.0 (50/61)	78.0 (39/50)	22.0 (11/50)		88.5 (54/61)	77.8 (42/54)	22.2 (12/54)	
fAUC ₀₋₂₄ :MIC ratio, three-group variable				0.038				0.04
≤0.9/ ^b ≥0.4 ^b	19.7 (12/61)	41.7 (5/12)	58.3 (7/12)		13.1 (8/61)	37.5 (3/8)	62.5 (5/8)	
>0.9 to ≤8/ ^b >0.4 to ≤8 ^b	54.1 (33/61)	72.3 (24/33)	27.3 (9/33)		60.7 (37/61)	73.0 (27/37)	27.0 (10/37)	
>8	26.2 (16/61)	87.5 (14/16)	12.5 (2/16)		26.2 (16/61)	87.5 (14/16)	12.5 (2/16)	
Log ₁₀ fAUC ₀₋₂₄ :MIC ratio, continuous variable	0.551 (−2.25, 1.73)	0.643 (−1.31, 1.73)	0.203 (−2.25, 1.28)	0.023	0.551 (−2.25, 1.73)	0.618 (−1.31, 1.73)	0.349 (−2.25, 1.28)	0.031
Log ₁₀ fAUC ₀₋₂₄ :MIC ratio, two-group variable	<−0.05/ ^b ≥−0.46 ^b	36.4 (4/11)	63.6 (7/11)	0.011	11.5 (7/61)	28.6 (2/7)	71.4 (5/7)	0.015
≥−0.05/ ^b ≥−0.46 ^b	82.0 (50/61)	78.0 (39/50)	22.0 (11/50)		88.5 (54/61)	77.8 (42/54)	22.2 (12/54)	
Log ₁₀ fAUC ₀₋₂₄ :MIC ratio, three-group variable				0.031				0.039
≤0/ ^b ≥−0.1 ^b	19.7 (12/61)	41.7 (5/12)	58.3 (7/12)		16.4 (10/61)	40.0 (4/10)	60.0 (6/10)	
>0 to ≤0.9/ ^b ≥−0.1 to ≤0.9 ^b	52.5 (32/61)	71.9 (23/32)	28.1 (9/32)		55.7 (34/61)	73.5 (25/34)	26.5 (9/34)	
>0.9	27.9 (17/61)	88.2 (15/17)	11.8 (2/17)		27.9 (17/61)	88.2 (15/17)	11.8 (2/17)	

^a Units for fAUC₀₋₂₄ are in mg/liter · h; units for MIC ranges are in mg/liter.
^b Values of thresholds defining subcategories of the independent variable based on the evaluation of clinical and microbiological response variables, respectively.

FIG 1 Estimated relationships between the probabilities of clinical (A) or microbiological (B) success and tigecycline $fAUC_{0-24}:MIC$ ratio, based on univariable logistic regression models ($P = 0.023$ and 0.031 , respectively). The solid lines represent the estimated logistic regression functions, while the dashed-dotted lines represent the upper and lower 95% pointwise confidence bounds. The histogram represents the distribution of observed $fAUC_{0-24}:MIC$ ratio values. The solid boxes on the estimated logistic regression functions represent the thresholds for $fAUC_{0-24}:MIC$ ratios of 0.9 and 0.35 for the probabilities of clinical and microbiological success, respectively, which were derived based on classification trees.

pharmacokinetics for patients with greater acuity and the greater potential for acquisition of resistant organisms in VAP patients, respectively, the percentages of successful clinical and microbiological responses and the distributions for the $fAUC_{0-24}:MIC$, and $fAUC_{0-24}:MIC$ ratio were compared. For VAP and non-VAP patients, the percentages of successful clinical responses were 52.2% (12/23) and 81.6% (31/38), respectively ($P = 0.018$); for microbiological responses, the percentages of successful responses were 47.8% (11/23) and 86.8% (33/38), respectively ($P = 0.002$). The median (minimum, maximum) $fAUC_{0-24}$ values for the 23 VAP and 38 non-VAP patients were 0.957 mg/liter $\cdot$ h (0.356, 4.02) and

FIG 2 Tigecycline MIC distribution stratified by VAP and non-VAP status (adapted with from reference 3 with permission of the publisher).

1.16 mg/liter $\cdot$ h (0.539, 3.50), respectively (Wilcoxon signed-rank test P value, 0.006). As shown in Fig. 2, the tigecycline MIC distribution for pathogens isolated in patients with VAP or non-VAP differed significantly (MIC_{50/90} values of 0.5/16 and 0.25/1 mg/liter; $P = 0.006$). The median (minimum, maximum) $fAUC_{0-24}:MIC$ ratios for VAP and non-VAP patients were 1.14 (0.00557, 16.1) and 5.69 (0.0490, 54.1), respectively ($P = 0.001$).

Multivariable analyses, which considered the inclusion of all independent variables, yielded models for both clinical and microbiological responses that contained altered mental status. However, given the lack of stability of these models when other variables, including $fAUC_{0-24}:MIC$ ratio, were considered, multivariable analyses were also conducted that excluded this variable. A summary of the three final multivariable logistic regression models for clinical or microbiological response is provided in Table 2. The final model for the clinical response contained albumin evaluated as a continuous variable and the two-group $fAUC_{0-24}:MIC$ ratio variable based on a threshold of 0.9 (model 1). The odds of clinical success were 13.0 times higher for every 1-g/dl increase in albumin ($P < 0.001$) and 8.42 times higher for patients with $fAUC_{0-24}:MIC$ ratios of ≥ 0.9 , compared to patients with $fAUC_{0-24}:MIC$ ratios that were < 0.9 ($P = 0.008$). For the microbiological response, the final model also contained albumin evaluated as a continuous variable and VAP status (model 2). The odds of microbiological success were 21.0 times higher for every 1-g/dl increase in albumin ($P < 0.001$) and 8.59 times higher for patients without VAP than those with VAP ($P = 0.003$). At the second step of the forward inclusion process, at which point VAP status entered the model, it was noted that MIC, when evaluated as a three-group variable, demonstrated the greatest significance among the independent variables other than VAP status. Given the above-described difference in MIC distribution by VAP status and, hence, the relationship between these two variables, a final model containing albumin as a continuous variable and MIC as a three-group variable was constructed (model 3) and is presented in Table 2.

The interactions between the two independent variables retained in each of the above-described final multivariable logistic regression models were explored. For models 1 and 2, neither

TABLE 2 Final multivariable logistic regression models for factors associated with clinical and microbiological success

Model description	Independent variable	Parameter estimate (SE)	Odds ratio (95% CI)	P value ^d
Model 1 for clinical response	Intercept	-7.30 (2.28)		
	Albumin ^a	2.56 (0.82)	13.0 (2.59, 65.1)	<0.001
	fAUC ₀₋₂₄ :MIC ratio of ≥ 0.9	2.13 (0.86)	8.42 (1.55, 45.7)	0.008
Model 2 for microbiological response	Intercept	-7.76 (2.56)		
	Albumin ^a	3.05 (1.03)	21.0 (2.82, 157)	<0.001
	Non-VAP ^b	-2.15 (0.78)	8.59 (1.85, 39.8)	0.003
Model 3 for microbiological response	Intercept	-8.30 (2.73)		
	Albumin	3.67 (1.11)	39.2 (4.39, 350)	0.001
	MIC, 0.5 or 1.0 mg/liter ^c	1.77 (1.02)	5.85 (0.79, 43.2)	0.16
	MIC, >1.0 mg/liter ^c	-1.35 (0.93)	0.259 (0.041, 1.62)	

^a Parameter estimates and odds ratios for albumin correspond to a 1 unit increase.^b Reference group represents the non-VAP patients.^c Reference group represents a MIC of <0.5 mg/liter.^d Based upon the likelihood ratio test. For model 3, Wald P values for MIC groups of 0.5–1.0 and >1.0 relative to 0.5 mg/liter were 0.08 and 0.14, respectively.

interaction was significant ($P = 0.80$ and $P = 0.22$, respectively). In contrast, the interaction between albumin and the three-group variable for MIC identified for model 3 was significant ($P = 0.019$). The high proportion of successful responses when albumin concentrations were elevated (which causes quasicomplete separation [1]), however, prevented estimation of parameters when this interaction was included in the model. Thus, for this reason, such a model is not presented in Table 2. Nonetheless, as presented in Table 3, the observed proportion of successful responses among cohorts of patients described by combinations of independent variables for this model effectively demonstrated the interaction. For albumin concentrations of <2.6 g/dl (the threshold for the two-group variable that was used to describe the microbiological response for cohorts of patients), the observed proportions of successful responses when MIC values were <0.5 mg/liter or 0.5 or 1.0 mg/liter, which were 0.5 and 0.67, respectively, were similar. However, a lower observed proportion of successful response (0.14) was evident with albumin concentrations of <2.6

g/dl and MICs that were >1.0 mg/liter. For albumin concentrations of ≥ 2.6 g/dl, higher proportions of successful responses were observed regardless of MIC. Thus, the significance of MIC as a predictor of microbiological response for model 3 was influenced by the association between microbiological response and MIC when albumin was low, even without consideration of the interaction between these variables.

The estimated logistic regression functions for the relationships between the probabilities of clinical or microbiological success and albumin relative to fAUC₀₋₂₄:MIC ratio evaluated as a two-group categorical variable or VAP status, based on the final multivariable models (models 1 and 2, respectively), are shown in Fig. 3A and B, respectively. A similar graphical display of the estimated logistic regression function for the relationship between the probability of microbiological response and albumin concentration relative to each category of the three-group MIC variable was not produced for model 3 due to our inability to obtain parameter estimates for such a model containing the interaction between albumin and MIC.

TABLE 3 Performance of multivariable logistic regression models for clinical and microbiological responses

Model description	Variable 1	Variable 2 ^a	No. of patients with successful response	Total no. of patients	Proportion with successful response	Avg model-estimated probability of successful response
Model 1 for clinical response	AUC ₀₋₂₄ :MIC ratio, <0.9	Albumin, <2.6 g/dl	1	7	0.14	0.21
	AUC ₀₋₂₄ :MIC ratio, <0.9	Albumin, ≥ 2.6 g/dl	3	4	0.75	0.64
	AUC ₀₋₂₄ :MIC ratio, ≥ 0.9	Albumin, <2.6 g/dl	12	21	0.57	0.57
	AUC ₀₋₂₄ :MIC ratio, ≥ 0.9	Albumin, ≥ 2.6 g/dl	27	29	0.93	0.93
Model 2 for microbiological response	Non-VAP	Albumin, <2.6 g/dl	9	13	0.69	0.67
	Non-VAP	Albumin, ≥ 2.6 g/dl	24	25	0.96	0.97
	VAP	Albumin, <2.6 g/dl	4	15	0.27	0.30
	VAP	Albumin, ≥ 2.6 g/dl	7	8	0.88	0.82
Model 3 for microbiological response	MIC, <0.5 mg/liter	Albumin, <2.6 g/dl	6	12	0.50	0.45
	MIC, <0.5 mg/liter	Albumin, ≥ 2.6 g/dl	18	20	0.90	0.93
	MIC, 0.5 or 1.0 mg/liter	Albumin, <2.6 g/dl	6	9	0.67	0.68
	MIC, 0.5 or 1.0 mg/liter	Albumin, ≥ 2.6 g/dl	9	9	1.0	0.99
	MIC, >1.0 mg/liter	Albumin, <2.6 g/dl	1	7	0.14	0.25
	MIC, >1.0 mg/liter	Albumin ≥ 2.6	4	4	1.0	0.82

^a Albumin was evaluated as a two-group variable for descriptive purposes. Final models (described in Table 2) were based on the continuous form of this variable.

FIG 3 Estimated relationships between the probability of clinical success and albumin concentration related to $fAUC_{0-24}$:MIC ratio, evaluated as a two-group categorical variable (A) or between the probability of microbiological success and VAP status (B).

The performance of each final logistic regression model was assessed by comparing the agreement between the observed proportion of patients with a successful response and the average model-estimated probability of a successful response among cohorts of patients described by combinations of independent variables. As shown in Table 3, there was good agreement between observed proportions and average model-estimated probabilities of successful responses, even for those cohorts for which the sample size was limited. For example, for model 1, the average model-estimated probability of clinical success and observed proportion of clinical successes for albumin concentrations of <2.6 and $fAUC_{0-24}$:MIC ratios of <0.9 were 0.21 and 0.14, respectively. Both the average model-estimated probability of clinical success and observed proportion of clinical successes were higher for $fAUC_{0-24}$:MIC ratios of <0.9 and albumin concentrations of ≥ 2.6 (0.64 and 0.75, respectively); these proportions were higher and identical for $fAUC_{0-24}$:MIC ratios of ≥ 0.9 and albumin concentrations of <2.6 (0.57) or when both conditions were optimized ($fAUC_{0-24}$:MIC ratio, ≥ 0.9 ; albumin, ≥ 2.6 [0.93]).

DISCUSSION

Using pharmacokinetic and clinical data from tigecycline-treated patients with HAP who were enrolled in a phase 3 clinical trial, the analyses described herein were conducted to evaluate pharmacologic and patient-specific determinants of clinical and microbiological responses. A number of interesting relationships were observed.

Whether evaluating the $fAUC_{0-24}$:MIC ratio as a continuous or categorical variable, univariable analyses revealed significant relationships for clinical and microbiological responses. As would be expected, given the concordance between clinical and microbiological responses, the estimated functions based on the univariable logistic regression models for each of these relationships were similar. Also, thresholds for the two-group variables for $fAUC_{0-24}$:MIC ratios based on classification trees were reasonably similar ($fAUC_{0-24}$:MIC ratios of ≥ 0.9 and ≥ 0.35 , respectively), with comparable observed percentages of successful responses for patients with $fAUC_{0-24}$:MIC ratios at and above each threshold (77.8 and 78.0%, respectively).

In addition to characterizing univariable PK-PD relationships between clinical and microbiological responses and the $fAUC_{0-24}$:MIC ratio, other significant and intuitive univariable relationships were noted for albumin, VAP status, and APACHE II score. Similar to the findings reported herein, lower albumin concentrations, VAP status, and increased APACHE II score have been found to be associated with poor outcome in patients with HAP (2, 11, 12, 13, 19). Like others (2), we also found that altered mental status was highly associated with response. However, given that this independent variable was thought to be a surrogate for nonresponse and that the consideration of this variable led to multivariable logistic regression models for which parameter estimates could not be reliably estimated, final models were derived without consideration of altered mental status.

Of the three final models for clinical or microbiological response presented in Table 2, each of which contained two independent variables, albumin was the most significant predictor in each model ($P \leq 0.001$). For the single model for clinical response, patients with $fAUC_{0-24}$:MIC ratios of ≥ 0.9 had an 8.42-higher odds of clinical success than patients with $fAUC_{0-24}$:MIC ratios of <0.9 ($P = 0.008$). For microbiological response, two final models are presented, the first retaining VAP status as the second independent variable and the second retaining MIC as a three-group variable when VAP was not considered. Given the differences in the MIC distributions by VAP status (as evident in Fig. 2 and as has been previously presented [3]) and, thus, the relationship between these two variables, the derivation of each of these final models for microbiological response was not surprising. Although the parameter estimates for MIC values of 0.5 or 1.0 relative to the <0.5 -mg/liter limit would suggest counterintuitive findings, as shown by observed proportions of microbiological successes by patient cohort in Table 3, the significance of MIC as a predictor of microbiological response was influenced in an intuitive manner by the association between microbiological response and MIC when albumin concentration was low. For patients with higher albumin concentrations, the impact of each subcategory of MIC on the proportion of microbiological success was indistinguishable.

The results of the univariable and multivariable analyses for clinical and microbiological responses described herein have two major implications for future HAP and VAP clinical trial designs.

As shown in Fig. 1A and B, the estimated probability of a successful response toward the upper and lower percentiles of the $fAUC_{0-24}:MIC$ ratio provides an estimate of drug effect, as the $fAUC_{0-24}:MIC$ ratio increases toward a maximal treatment effect or as the $fAUC_{0-24}:MIC$ ratio decreases toward the no-treatment effect. The span of the probability of a successful response closely approximates the treatment effect (i.e., the maximal benefit of therapy in a given patient population, which in this case is approximately 70%). Such an estimate provides the critical missing data needed to design noninferiority studies with appropriate statistical power, which in turn obviate the need for superiority study designs. Moreover, these data make it possible to estimate the no-treatment response rate without exposing patients to any risk (morbidity or mortality) incurred by conducting superiority studies that are placebo controlled or which utilize suboptimal dose ranges or comparator regimens (4).

Second, albumin in the context of either the $fAUC_{0-24}:MIC$ ratio or MIC value was a highly significant predictor of clinical and microbiological responses. As shown in Fig. 3A, patients with adequate drug exposure ($fAUC_{0-24}:MIC$ ratio, ≥ 0.9) but a very low baseline albumin concentration (2 g/dl) had a model-predicted probability of clinical success of 0.35, while those with adequate drug exposure ($fAUC_{0-24}:MIC$ ratio, < 0.9) and normal baseline albumin concentrations (4 g/dl) had a model-predicted probability of clinical success approaching 1.0. Moreover, the model-predicted probability of clinical success approached less than 0.1 for patients with inadequate drug exposure and very low baseline albumin concentrations, while those patients with inadequate drug exposure but normal baseline albumin concentrations had a model-predicted probability of clinical success that exceeded 0.9. Given the influence of albumin on clinical and microbiological responses to therapy, consideration should be given for utilizing albumin to screen for patients most likely to benefit from antimicrobial chemotherapy.

One limitation of the analyses described herein was the sample size of the patient population evaluated. The evaluable population, which included clinically and microbiologically evaluable patients with sufficient PK data, was limited. Thus, the ability to evaluate the impact of pathogen group on the PK-PD relationship for efficacy was also limited. Given the constraints of sample size, the multivariable models described herein could not be expanded to include additional independent variables.

In conclusion, we identified PK-PD relationships for $fAUC_{0-24}:MIC$ ratio or MIC and clinical and microbiological responses in the context of response modifiers. Important response modifiers included albumin and VAP status, the latter of which was associated with an elevated baseline pathogen MIC value. Such findings will be useful in the design of and statistical powering of future clinical trials of this patient population.

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