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Short Communication

Clinical response and mortality in tigecycline complicated intra-abdominal infection and complicated skin and soft-tissue infection trials☆

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ABSTRACT

An imbalance in all-cause mortality was noted in tigecycline phase 3 and 4 comparative clinical trials across all studied indications. We investigated clinical failure and mortality in phase 3 and 4 complicated skin and soft-tissue infection (cSSTI) and complicated intra-abdominal infection (cIAI) tigecycline trials using descriptive analyses of a blinded adjudication of mortality and multivariate regression analyses. Attributable mortality analyses of cSSTI revealed death due to infection in 0.1% of each treatment group ($P = 1.000$). In cIAI, there were no significant differences between tigecycline (1.2%) and comparator (0.7%) subjects who died due to infection ($P = 0.243$). For cIAI clinical failure, treatment interaction with organ dysfunction was observed with no difference observed between clinical cure for tigecycline (85.4%) and comparator (76.7%) treatment groups (odds ratio = 0.58, 95% confidence interval 0.28–1.19). Tigecycline-treated subjects had more adverse events of secondary pneumonias (2.1% vs. 1.2%) and more adverse events of secondary pneumonias with an outcome of death (0.5% vs. 0.1%). These analyses do not suggest that tigecycline is a factor either for failure (cSSTI and cIAI studies) or for death (cIAI studies).

1. Introduction

An imbalance in all-cause mortality has been noted in tigecycline phase 3 and 4 comparative clinical trials across most studied indications, including the non-approved indications [hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia, and diabetic foot infection studies] [1,2]. Deaths were attributed to infection (i.e. worsening or complications of the infection) or underlying co-morbidities [2]. A phase 2 trial examining higher doses for the treatment of HAP suggested that the dose of tigecycline may have played a role in the poor clinical responses in the previously conducted phase 3 HAP trial [3,4]. Different published meta-analyses of study-level data suggest decreased clinical efficacy as a possible explanation for this imbalance in mortality [5,6].

In this analysis, clinical failure and mortality in complicated skin and soft-tissue infection (cSSTI) and complicated intra-abdominal infection (cIAI) were explored using descriptive analyses of a blinded adjudication of mortality and multivariate regression analyses. The analyses were used to investigate the association of baseline factors, including severity of illness at study entry and treatment assignment, with clinical failure and mortality.

2. Methods

2.1. Studies

Tigecycline was given as a 100 mg loading dose, followed by 50 mg every 12 h for a maximum of 14 days in all studies. Comparator treatments varied by study and infection type [7–14].

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2.2. Analysis methods

Several analyses including attributable mortality analysis and logistic regression were conducted to understand and evaluate the imbalance in mortality.

2.2.1. Attributable mortality

Medical records of subjects who died in the cSSTI and cIAI trials were reviewed by three independent experts. The sponsor provided blinded subject narratives pertaining to the death of the study subjects. Subject narratives included: demographic data; relevant medical history, including initial symptoms and clinical process leading to study inclusion; concomitant medication use; dates of study drug administration; adverse event (AE) information; Acute Physiology and Chronic Health Evaluation (APACHE) II score (cIAI only) at study inclusion; clinical disease course and relevant microbiology; and laboratory data. Death certificates and available autopsy results also were provided.

Individual expert judgement was applied to attribute the cause of death. Deaths were categorised into predefined categories: (i) death due to infection—death was related to the primary infection; possible treatment failure; (ii) death not due to primary infection—e.g. an AE; and (iii) death with infection—death was unrelated to the primary infection but occurred while undergoing treatment. The individual reviewer was blinded to the adjudications of the other reviewers. For final categorisation, agreement on the classification between at least two reviewers was needed. If a consensus was not reached, the data were excluded. Following the review process, the results were aggregated and unblinded.

2.2.2. Multivariate logistic regression

Multivariate logistic regression was used to identify factors in each infection type that were significantly related to clinical failure in the clinically evaluable (CE) population. An analysis to identify factors related to mortality in the modified intent-to-treat (mITT) population (i.e. subjects receiving at least one dose of study drug) was performed.

Clinical response definitions were based on the clinical trial definitions in each protocol [7–14]. Baseline factors included in the analyses were demographics, medical history, infection and surgical variables, laboratory parameters and severity of infection, and the subject's condition at enrolment. For the cIAI analysis, organ dysfunction at baseline, defined as creatinine >2.0 μmol/L, international normalised ratio >1.5 or activated partial thromboplastin time >60 s, platelets <100,000 10^9/L and total bilirubin >70 μmol/L (not used for subjects with complicated cholecystitis), was also evaluated.

Potential interactions between treatment and each of the covariates of interest were evaluated in univariate models with outcomes of failure and mortality. Interactions that met the screening criteria of a *P*-value of <0.05 were chosen for inclusion in the final model-building process. A bootstrap approach was used to select variables for the final model [15]. Variables were identified for inclusion in the final model based on selection in ≥50% of 1000 bootstrap samples, where the model for each bootstrap sample was selected by backward variable elimination.

2.2.3. Adverse events

Using the clinical safety database, pneumonia AEs and serious AEs associated with mortality were descriptively compared between treatment arms.

2.3. Ethics

This was a secondary analysis of clinical trials; detailed institutional review board approval and informed consent were not applicable.

3. Results

A total of 2216 subjects received tigecycline (cSSTI, $n = 834$; cIAI, $n = 1382$) and 2206 received a comparator treatment (cSSTI, $n = 813$; cIAI, $n = 1393$).

3.1. Attributable mortality

Of the 91 deaths evaluated, there were 54 deaths in the tigecycline group and 37 in the comparator group. In the cSSTI trials, there were 18 deaths, with 12 deaths occurring in the tigecycline group and 6 in the comparator group. In the cIAI trials, 42 deaths occurred with tigecycline and 31 with comparator treatment. A consensus could not be reached in five cases; these deaths were excluded from further analysis before unblinding. After blinding was broken, it was determined that all five cases were in the tigecycline cIAI treatment group.

A summary of the attributable mortality classifications is shown in Table 1. For the cSSTI indication, the majority of tigecycline and comparator cases were not attributed to infection. One case in each treatment group was due to infection; the tigecycline case was associated with septic shock at enrolment and myocardial infarction.

For the cIAI indication, differences between treatment groups were observed in the classification schema. A greater number of comparator-treated subjects died not due to infection (1.4% vs. 1.1%; $P = 0.497$) and a greater number of tigecycline-treated subjects died with infection (0.4% vs. 0.1%; $P = 0.068$). A numerically higher number of tigecycline-treated subjects ($n = 16$; 1.2%) than comparator-treated subjects ($n = 10$; 0.7%) died due to infection ($P = 0.243$); however, of those, more tigecycline-treated subjects were assessed as having confounding factors ($P = 0.001$). Confounding factors in the tigecycline group included septic shock at enrolment ($n = 6$), inadequate source control ($n = 8$) and untreated candidiasis ($n = 1$). Confounding factors in the comparator group

Table 1
Attributable mortality analysis: relationship of death and infection.

	Tigecycline [*n*/*n* (%)]	Comparator [*n*/*n* (%)]	*P*-value[a]
cSSTI (*N* = 1647)			
Death due to infection	1/834 (0.1)	1/813 (0.1)	1.000
Confounding factor	1/1 (100)[b]	0/1 (0.0)	1.000
Death with infection	2/834 (0.2)	0/813 (0.0)	0.500
Death not due to infection	9/834 (1.1)	5/813 (0.6)	0.422
cIAI (*N* = 2775)[c]			
Death due to infection	16/1382 (1.2)	10/1393 (0.7)	0.243
Confounding factor	14/16 (87.5)[d]	2/10 (20.0)[e]	0.001
Death with infection	6/1382 (0.4)	1/1393 (0.1)	0.068
Death not due to infection	15/1382 (1.1)	20/1393 (1.4)	0.497

cSSTI, complicated skin and-soft tissue infection; cIAI, complicated intra-abdominal infection.

[a] Fisher's exact test (two-tailed).

[b] Septic shock at enrolment and myocardial infarction.

[c] Five missing patients in the tigecycline group represent the cases where there was no agreement among the adjudicators; these patients were excluded from the analysis.

[d] Septic shock at enrolment, inadequate source control and untreated candidiasis.

[e] Septic shock at enrolment and inadequate source control.

Table 2
Multivariate logistic regression modelling in subjects with complicated skin and-soft tissue infection (cSSTI) and complicated intra-abdominal infection (cIAI).

Variable	Adjusted OR	95% CI	*P*-value
Clinical failure (CE population)			
cSSTI			
History of diabetes	1.93	1.35–2.77	<0.001
Haemoglobin	0.89	0.82–0.98	0.012
Elevated WBC count	1.54	1.14–2.07	0.005
Total protein	0.87	0.74–1.02	0.086
Region (vs. Asia)			
South America	0.31	0.14–0.69	<0.001
North America	0.87	0.50–1.49	<0.001
India	0.48	0.21–1.09	<0.001
Europe	0.37	0.21–0.65	<0.001
cIAI			
APACHE II score	1.90	1.36–2.66	<0.001
Baseline AST/ALT >ULN	1.25	0.93–1.68	0.132
BMI	1.45	1.11–1.89	0.006
Total protein	0.82	0.71–0.94	0.004
Source of infection (vs. appendix)			
Gallbladder	0.29	0.15–0.55	<0.001
Intra-abdominal abscess	1.26	0.75–2.12	<0.001
Large bowel	1.47	1.00–2.18	<0.001
Small bowel	1.16	0.67–2.02	<0.001
Stomach/duodenum	0.68	0.37–1.25	<0.001
Increased probability of controlling source infection[a]	0.73	0.62–0.86	<0.001
Size of abscess[b]	1.13	1.00–1.28	0.046
Nosocomial infection	1.57	0.95–2.60	0.082
ICU within 24 h after surgery	1.51	1.07–2.12	0.018
Baseline vasopressor use	1.45	0.71–2.99	0.309
Type of surgery	0.77	0.61–0.96	0.023
Non-susceptible Gram-negative pathogen[c]	2.07	1.09–3.90	0.025
Non-susceptible anaerobic pathogen	1.78	1.11–2.85	0.018
Presence of *Enterococcus* spp.	1.43	0.99–2.07	0.055
Mortality (cIAI mITT population)			
Age (years)	1.76	1.46–2.11	<0.0001
Total protein	0.70	0.55–0.88	0.003
Source of infection (vs. appendix)			
Gall bladder	0.61	0.15–2.49	0.001
Intra-abdominal abscess	2.82	0.95–8.39	0.001
Large bowel	4.60	1.79–11.83	0.001
Small bowel	6.27	2.22–17.71	0.001
Stomach/duodenum	3.31	1.14–9.63	0.001
Increased probability of controlling source infection[a]	0.69	0.53–0.89	0.005
Size of abscess[b]	1.27	1.01–1.59	0.041
ICU within 24 h after surgery	1.85	1.02–3.37	0.044
Baseline vasopressor use	2.57	1.23–5.37	0.012

OR, odds ratio; CI, confidence interval; CE, clinically evaluable; WBC, white blood cell; APACHE, Acute Physiology and Chronic Health Evaluation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal; BMI, body mass index; ICU, intensive care unit; mITT, modified intent-to-treat.

[a] 1, <25%; 2, 25–49%; 3, 50–74%; 4, 75–95%; and 5, >95%.

[b] 0, no abscess; 1, <10 mL; 2, 10–100 mL; and 3, >100 mL.

[c] Excludes *Pseudomonas* spp.

included septic shock at enrolment ($n = 1$) and inadequate source control ($n = 1$). Confounding factors, in particular septic shock and inadequate surgical source control, suggested a further examination of baseline characteristics, including severity at presentation.

3.2. Multivariate logistic regression

3.2.1. Complicated skin and soft-tissue infection

A total of 1238 CE subjects (tigecycline, $n = 631$; comparator, $n = 607$) from three cSSTI trials were included in the clinical response modelling. Subjects had similar baseline demographics (Supplementary Table S1). Clinical diagnosis was similar between groups, with the majority of infections attributed to deep soft-tissue infection.

Supplementary Table S1 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijantimicag.2015.05.012

A failure model was run on the CE populations. The initial analysis evaluated treatment, 23 additional variables (Supplementary Table S2) and three treatment interactions [presence of fever, elevated white blood cell (WBC) count and presence of Gram-negative pathogens (except *Pseudomonas aeruginosa*)]. Following backward elimination in 1000 bootstrap re-samples, eight variables remained (history of diabetes, diagnosis, presence of fever, haemoglobin, total protein, region, treatment and elevated WBC count). Due to model convergence issues, the model was then further reduced by repeating the bootstrapping analysis methods. The final model was based on selecting variables occurring with a frequency >50% and included diabetes, haemoglobin, total protein, region and elevated WBC count. The final model included these variables in addition to forcing treatment into the model. History of diabetes (1.93) and elevated WBC count (1.54) were identified as variables [odds ratio (OR)] associated with clinical failure (Table 2). Treatment was not included in the final model for failure by the bootstrapping process because it was not selected as an important factor (i.e. not selected in >50% of the models). Treatment was forced into the final logistic models [OR = 1.21, 95% confidence interval (CI) 0.87–1.69] to give an estimate of the treatment effect while adjusting for other important covariates.

Table 3
Rates of cure by organ dysfunction in subjects with complicated intra-abdominal infection (cIAI) (clinically evaluable population).

Variable	Tigecycline cure [*n*/*n* (%)]	Comparator cure [*n*/*n* (%)]	OR (95% CI)[a]
Organ dysfunction			
Yes	123/144 (85.4)	112/146 (76.7)	0.58 (0.28–1.19)
No	827/998 (82.9)	886/1013 (87.5)	1.40 (1.05–1.88)

OR, odds ratio; CI, confidence interval.
[a] The OR and 95% CI obtained from final logistic model.

Supplementary Table S2 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijantimicag.2015.05.012

A multivariate mortality analysis was not conducted because of the limited number of deaths (18/1647).

3.2.2. Complicated intra-abdominal infection

A total of 2309 CE subjects (tigecycline, $n = 1149$; comparator, $n = 1160$) from five cIAI trials were included in the clinical failure modelling, and 2775 subjects who received at least one dose of study drug (tigecycline, $n = 1382$; comparator, $n = 1393$) were included in the mortality modelling. Subjects had similar baseline demographics in the mITT population (Supplementary Table S3) and the CE population (data not shown). Vasopressor use at baseline was numerically higher in the tigecycline group (54/1382; 3.9%) versus the comparator group (37/1393; 2.7%) ($P = 0.064$).

Supplementary Table S3 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijantimicag.2015.05.012

In the initial clinical failure model, treatment, 24 variables (Supplementary Table S4) and two treatment interactions (vasopressor use and presence of organ dysfunction) were tested. Using bootstrapping, 17 variables and one treatment interaction were identified for continued evaluation: non-susceptible anaerobic pathogen; APACHE II score; elevated liver function tests; body mass index; presence of a non-susceptible Gram-negative pathogen other than *P. aeruginosa*; nosocomial infection; organ dysfunction; admission to the intensive care unit (ICU); vasopressor use; total protein; region; size of abscess; source of infection; decreased probability of controlling source infection as assessed by the surgeon; antibiotic treatment; type of surgery; and treatment interaction with organ dysfunction. A multivariate analysis (Table 2) identified several independent variables (OR) associated with clinical failure. Laparotomy was protective relative to laparoscopic and percutaneous procedures.

Supplementary Table S4 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijantimicag.2015.05.012

Data regarding an organ dysfunction interaction effect with treatment are shown in Table 3. A numerically higher number of tigecycline-treated subjects were cured relative to comparator-treated subjects, but the differences were not significant (85.4% vs. 76.7%). Subjects without organ dysfunction were more likely to be cured with comparator treatment than with tigecycline. No association between treatment failure and vasopressor use was identified. The vast majority of subjects in both groups were not receiving vasopressor treatment; however, tigecycline cured 27/35 subjects (77.1%) with baseline vasopressor use compared with 12/25 (48.0%) of comparator-treated subjects.

Treatment group and the same 24 variables tested in the clinical failure model (Supplementary Table S4) were initially selected for evaluation in the mortality analysis. The selection of variables was narrowed to eight following bootstrap elimination: age; care in the ICU at baseline; probability of controlling source infection; vasopressor use; total protein; region; size of abscess; and source of infection. No significant treatment interactions were noted. Independent variables (OR) associated with mortality in the multivariate analysis are listed in Table 2. Treatment was forced into the final logistic model (OR = 1.25, 95% CI 0.73–2.14) for mortality to give an estimate of the treatment effect while adjusting for other important covariates.

3.3. Adverse events

The reasons for death in subjects whose death was not related to infection are listed in Supplementary Table S5. An evaluation of the reasons for death demonstrated a numerically higher number of deaths related to pneumonia in tigecycline-treated subjects. Further review of the clinical safety database demonstrated for the cSSTI indication that the overall number of subjects who were reported as having pneumonia during the study was 4/834 (0.5%) among tigecycline-treated subjects and 1/813 (0.1%) among comparator-treated subjects. No deaths were reported among these subjects and three of the four tigecycline pneumonias occurred after therapy completion. For the cIAI indication, 29/1382 (2.1%) tigecycline-treated subjects were reported as having pneumonia compared with 17/1393 (1.2%) comparator-treated subjects. Among subjects with cIAIs, death occurred in 7/1382 (0.5%) tigecycline-treated and 1/1393 (0.1%) comparator-treated subjects reported as having pneumonia. Pneumonia developed while on study drug in 22/29 subjects (75.9%) in the tigecycline group and 10/17 subjects (58.8%) in the comparator group. Vomiting did not appear to contribute to the development of pneumonia on study, as only 2/29 (6.9%) tigecycline-treated and 3/17 (17.6%) comparator-treated subjects reported vomiting before the episode of pneumonia.

Supplementary Table S5 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijantimicag.2015.05.012

4. Discussion

This study provides valuable insights into clinical response, mortality and complicating AEs. For the cSSTI indication, multivariate modelling suggested that diabetes and elevated WBC count, but not treatment assignment, were associated with clinical failure. Blinded attributable mortality analysis suggested a low attributable fraction of subjects with cSSTI who died due to infection. Combined with the overall demonstration of non-inferiority with comparator treatments in three appropriately powered studies [7,9,12], the cSSTI deaths appear related more to the subject's underlying co-morbid state and not due to poor clinical response.

Similar conclusions can be drawn for the cIAI indication. Multivariate clinical response modelling did not suggest that treatment assignment was associated with clinical failure. A treatment assignment interaction with organ dysfunction was identified in multivariate clinical response modelling; however, tigecycline clinical success was higher in subjects with organ dysfunction and lower in those without organ dysfunction. Although baseline vasopressor use was not associated with clinical failure, tigecycline-treated subjects with baseline vasopressor use had numerically higher clinical success than comparator-treated subjects. Efficacy did not worsen in subjects with baseline markers of more severe cIAI; this is counterintuitive if efficacy in cIAI was associated with mortality, as was observed in the phase 3 HAP trial [2,3].

Mortality modelling identified multiple factors associated with death, but not tigecycline that was forced into the model. Similarly, attributable mortality among subjects who died of primary infection in the cIAI studies showed no difference among treatments. Combined with the four powered phase 3 and 4 cIAI trials that demonstrated the non-inferiority of tigecycline to the comparator regimens [8,10,11,13], these results suggest that deaths were less related to clinical failure and that other factors or patient co-morbidities were more likely to contribute to death.

One of the most interesting cIAI observations gleaned from the attributable mortality analysis and safety database review was the observation of more pneumonias in tigecycline-treated subjects. There were few deaths, but a larger disparity in subjects with pneumonia developing between tigecycline- and comparator-treated subjects. Although pneumonia is a well recognised complication of cIAI, the excess number of pneumonia cases in tigecycline-treated subjects remains puzzling. Although speculative at best, the lack of efficacy in the phase 3 HAP trial may suggest that tigecycline failed to prevent or treat emergent pneumonia at the standard dose given in cIAI [3].

The current analysis has some limitations. First, the analyses were post hoc and the data source was clinical trials that were not specifically designed to answer these proposed questions. Second, no attributable mortality classification has been validated; however, this schema was used to better understand the subject deaths in relation to the primary infection under treatment. Finally, the limited number of deaths among patients with cSSTI precludes a multivariate mortality analysis in this population.

5. Conclusions

In this study, modelling and attributable mortality analyses suggested that tigecycline is not a significant factor either for failure (cSSTI and cIAI studies) or for death (cIAI studies).

The increased medical need represented by the growing impact of multidrug-resistant infections and the current lack of alternative or new antibiotics suggests that tigecycline benefit–risk continues to be positive; however, the all-cause mortality difference should be considered when using tigecycline.

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Competing interests

RDM, JLY, MW, STR and AQ are employees of and own stock in Pfizer Inc.; PCM is a former employee of Pfizer Inc.; MB serves on scientific advisory boards for and has received funding for travel or speaker honoraria from Pfizer Inc. CW declares no competing interests.

Ethical approval

Not required.

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