International Journal of Antimicrobial Agents 41 (2013) 463–467

Contents lists available at SciVerse ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Short communication

All-cause mortality imbalance in the tigecycline phase 3 and 4 clinical trials

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ARTICLE INFO

Article history:
Received 31 July 2012
Accepted 31 January 2013

Keywords:
Tigecycline
Mortality
All-cause
Glycylcycline
Meta-analysis
Patient-level data

ABSTRACT

In 12 of 13 phase 3 and 4 comparative clinical trials, all-cause mortality was higher in the tigecycline group versus the comparator group. Study-level mortality risk differences were pooled using a random-effects meta-analysis. Statistical models evaluated the association between patient-level all-cause mortality and baseline factors using logistic regression, recursive partitioning [classification and regression tree (CART) analysis] and survival techniques. The estimated risk difference (tigecycline minus comparator) in all-cause mortality from the meta-analysis was 0.6% (95% confidence interval 0.1–1.2%). Statistical modelling identified baseline bacteraemia associated with mortality only in the tigecycline group. In patients with ventilator-associated pneumonia (VAP) and baseline bacteraemia, mortality was 50.0% (9/18) for tigecycline versus 7.7% (1/13) for the comparator group. Study-level and patient-level analyses have identified that patients in the hospital-acquired pneumonia trial, particularly those with VAP with baseline bacteraemia, were at a higher risk of clinical failure and mortality.

1. Introduction

Tigecycline is a glycylcycline antibiotic that was developed to restore the broad spectrum of activity and clinical utility to the tetracycline class of antibiotics. The tigecycline clinical development programme investigated the efficacy and safety of tigecycline in hospitalised patients with serious infections. Tigecycline is approved for the treatment of complicated skin and skin-structure infections, complicated intra-abdominal infections (cIAIs) and community-acquired pneumonia (CAP). However, tigecycline did not meet the primary endpoints in hospital-acquired pneumonia (HAP) and diabetic foot infection trials.

An unexpected observation was the numerical increase in all-cause mortality in tigecycline-treated patients in phase 3 and 4 clinical trials [1]. Recently, several independent meta-analyses on tigecycline all-cause mortality have been published, all of which were based on study-level data only [2–5]. This article is the first to present patient-level data that would be helpful to better understand these findings [4].

2. Materials and methods

2.1. Studies

Tigecycline was studied in 14 phase 3 and 4 trials between August 2001 and September 2008, including 13 comparative studies. The study design, comparator and number of patients treated have been accurately reported elsewhere [2]; however, six additional patients (two tigecycline, four comparator) were included in our analysis to capture all patients who died.

2.2. Patient population

Unless otherwise noted, these analyses were based on the modified intention-to-treat (safety) population, which includes all patients who were randomised and received at least one dose of study medication.

2.3. Risk factors

Demographic and baseline variables examined as potential factors that could affect mortality included age, co-morbidities, mortality prediction scores [Acute Physiology and Chronic Health Evaluation (APACHE) II score where available], infection type, prior antibiotic failure, baseline pathogen and minimum inhibitory

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0924-8579
http://dx.doi.org/10.1016/j.ijantimicag.2013.01.020

Table 1
Demographic and baseline characteristics in the modified intention-to-treat population.

Characteristic[a]	*P* value[b]	Mortality subgroup			
		Died		Survived	
		Tigecycline (*n* = 150)	Comparator (*n* = 110)	Tigecycline (*n* = 3638)	Comparator (*n* = 3536)
Age (years) (mean)	0.630[f]	65.96	66.90	50.96	50.71
Male sex [*n* (%)]	0.698[g]	91 (60.7)	70 (63.6)	2303 (63.3)	2288 (64.7)
APACHE II score (mean)[c]	0.864[f]	13.43	13.57	7.39	7.36
Baseline albumin (g/L) (mean)[d]	0.953[f]	25.38	25.44	34.45	34.58
Alkaline phosphatase (U/L) (mean)	0.301[f]	155.62	140.11	125.11	123.45
Creatinine (μmol/L) (mean)[e]	0.906[f]	97.32	98.05	85.30	85.62
WBC (10^9/L) (mean)	0.023[f]	12.79	14.98	15.21	12.34
History of diabetes [*n* (%)]	0.246[g]	42 (28.0)	23 (20.9)	1013 (27.8)	940 (26.6)
COPD [*n* (%)]	0.254[g]	23 (15.3)	23 (20.9)	154 (4.2)	145 (4.1)
CHF [*n* (%)]	0.603[g]	21 (14.0)	18 (16.4)	129 (3.5)	119 (3.4)
Prior antibiotic failure [*n* (%)]	0.775[g]	37 (24.7)	29 (26.4)	605 (16.6)	533 (15.1)
Total protein (g/L) (mean)	0.363[f]	54.47	55.89	65.95	65.83
BMI (mean)	0.530[f]	25.05	25.60	26.79	26.72

APACHE, Acute Physiology and Chronic Health Evaluation; WBC, white blood cells; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; BMI, body mass index.
[a] Baseline information was not available for all patients. There was no imputation for missing values.
[b] *P*-values represent comparisons between incidences of tigecycline deaths and comparator deaths.
[c] Not all studies collected APACHE II score data.
[d] Albumin level was not collected in the phase 4 trials.
[e] To convert to mg/dL, divide by 88.4.
[f] One-way analysis of variance with treatment as factor.
[g] Fisher's exact test *P*-value (two-tailed).

concentrations (MIC), baseline concomitant bacteraemia and baseline laboratory data.

2.4. Statistical methods

A DerSimonian and Laird random-effects model meta-analysis [6], with trial as the random effect, was used to estimate an overall risk difference and 95% confidence interval (CI). The risk difference was chosen as the most meaningful quantity from a public health perspective. Logistic regression and classification and regression tree (CART) models were used to explore the influence and relative strength of various predictors on mortality. From separate logistic regression models for tigecycline-treated patients and comparator-treated patients, χ^2 minus degrees of freedom statistics were used to assess the relative importance of individual predictors. Larger values implied greater importance. Kaplan–Meier survival curves were used to qualitatively examine the relative timing of events. Unless otherwise noted, statistical significance refers to a two-sided type 1 error of 0.05. Computations were carried out in R v.2.10 language and supplemental libraries (http://www.R-project.org) and SAS v.9.2 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Study-level results

In the 13 phase 3 and 4 comparative studies, 4.0% (150/3788) of tigecycline-treated patients and 3.0% (110/3646) of comparator-treated patients died. In a pooled analysis of these trials, based on a random-effects model by trial weight, the adjusted risk difference for all-cause mortality was 0.6% (95% CI 0.1–1.2%) between tigecycline-treated patients and comparator-treated patients. The 30-day all-cause mortality was 3.2% and 2.6% in tigecycline-treated patients and comparator-treated patients, respectively (adjusted risk difference 0.4, 95% CI −0.1 to 0.9). There were no statistically significant differences between treatment groups by infection type [7]. The highest mortality rates in tigecycline-treated patients were observed in the ventilator-associated pneumonia (VAP) subgroup of the HAP trial (19.1%) and in the Resistant Pathogen (RP) 307 trial (8.6%).

3.2. Baseline demographics

Baseline demographics of patients who did and did not die in each treatment group are presented in Table 1. The data presented are representative of risk factors of potential importance for mortality and evaluated in the multivariate analyses. Differences in baseline characteristics were observed between patients who died and those who did not die; however, for most characteristics, the tigecycline and comparator treatment groups were similar. In general, patients who died were older, had higher APACHE II scores, lower albumin levels and higher creatinine levels. A greater number of tigecycline-treated patients versus comparator-treated patients with diabetes died, but the difference was not statistically significant. Baseline white blood cell values were statistically lower in tigecycline-treated patients who died; however, the clinical significance of the difference is unclear.

3.3. Baseline pathogens

Baseline pathogens and MICs were examined in patients who died. The frequencies of patients who died without a known baseline pathogen were similar between the tigecycline (30.7%) and comparator (30.9%) treatment groups. More comparator-treated patients died with baseline isolates of *Acinetobacter calcoaceticus/baumannii* (10.0% vs. 6.0%), *Pseudomonas aeruginosa* (9.1% vs. 7.3%) and meticillin-sensitive *Staphylococcus aureus* (13.6% vs. 8.7%), whilst a greater number of tigecycline-treated patients with baseline isolates of *Escherichia coli* (17.3% vs. 13.6%), *Klebsiella pneumoniae* (14.7% vs. 9.1%) and meticillin-resistant *S. aureus* (12.0% vs. 9.1%) died. Overall, the tigecycline MIC_{90} (MIC that inhibited growth of 90% of strains) for pathogens except *P. aeruginosa* was ≤1.0 μg/mL for tigecycline-treated patients. The MIC_{90} for *K. pneumoniae* in patients who died was 1.0 μg/mL; however, the MIC_{90} was 2.0 μg/mL in patients with HAP who died.

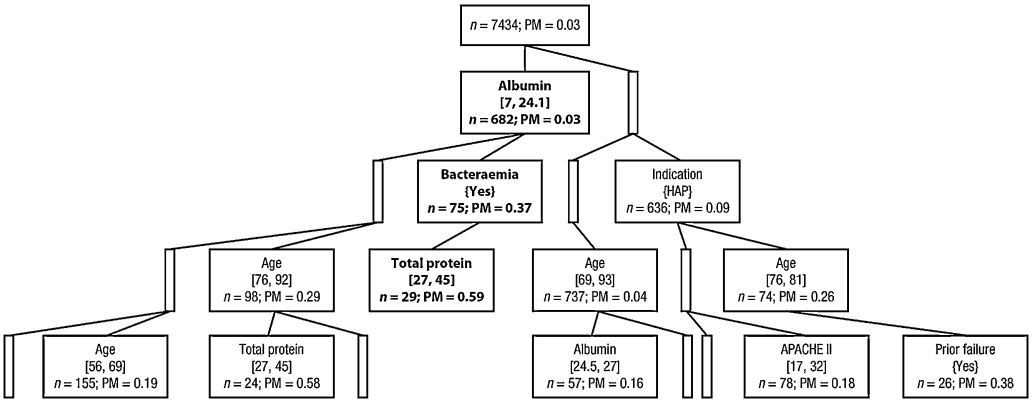

Fig. 1. Classification and regression tree (CART) analysis shows significant predictors with the predicted probability of mortality (PM) and with number of deaths (*n*) associated with specific factor ranges (continuous variables) or levels (categorical variables). Albumin normal range, 35–55 g/L; total protein normal range, 55–80 g/L. HAP, hospital-acquired pneumonia; APACHE II, Acute Physiology and Chronic Health Evaluation II scoring system.

3.4. Survival analyses

Kaplan–Meier analyses were performed for the 13 studies pooled (data not shown) and a large separation occurred after 40 days. Kaplan–Meier analyses by indication suggested differences in the risk of death among indications, with the highest risk (i.e. greater slope) in the HAP and RP 307 studies.

A categorical distribution of the timing of death relative to both the first and last dose was also performed. Death within 2 days (5.3% vs. 6.4%) and within 7 days (20.7% vs. 21.8%) of first dose was similar between the tigecycline and comparator-treatment groups, respectively. The greatest early difference between the tigecycline and comparator groups occurred between Days 8 and 14, with 29.3% and 26.6% of deaths, respectively. More tigecycline-treated patients died ≥15 days after the last dose of therapy (28.7% vs. 22.7% for comparator-treated patients) and more tigecycline-treated patients in this group of late deaths were deemed a clinical cure at the test-of-cure visit by the investigators (8.7% vs. 2.7% for comparator-treated patients). A review of late deaths revealed multiple aetiologies and not late deaths owing to the primary infection under study.

3.5. Risk factor analyses

Logistic regression analyses and CART modelling each identified a similar set of risk factors. Fig. 1 shows the CART model with potential predictors of mortality for all patients in the tigecycline trials. Low albumin, baseline bacteraemia, low total protein, patients with HAP, older age, higher APACHE II score and prior antibiotic failure were associated with mortality. For example, in the CART branch in bold in Fig. 1, 29 patients with low albumin levels (range 7.0–24.1 g/L), baseline bacteraemia and low total protein (range 27.0–45.0 g/L) were associated with a probability of death of 0.59. Treatment assignment did not emerge as a risk factor in either the CART modelling or logistic regression analyses ($P = 0.3746$) of the pooled data.

A review of APACHE II scores by indication did not reveal lower clinical efficacy in tigecycline-treated patients with a higher probability of mortality, with the exception of patients with VAP. In the cIAI phase 3 and 4 trials, tigecycline cured 20/29 patients (69.0%) with APACHE II scores >15 in the clinically evaluable population compared with 19/32 (59.4%) comparator-treated patients. In the HAP trial, cure rates in patients with APACHE II scores >15 were 29/58 (50.0%) and 36/57 (63.2%) for the tigecycline and imipenem/cilastatin regimens, respectively, with greater disparity in clinical success in patients with VAP (36.0% vs. 58.3%). Finally, in the RP 307 trial, 3/7 (42.9%) tigecycline-treated patients and 2/4 (50.0%) vancomycin-treated patients with APACHE II scores >15 were cured. Fine score was not modelled; however, in patients with CAP, tigecycline cured 55/62 patients (88.7%) with Fine scores of IV–V in the clinically evaluable population compared with 51/65 (78.5%) levofloxacin-treated patients.

Logistic regression models also were developed separately for tigecycline-treated patients and comparator-treated patients. Rank ordering of identified risk factors showed similarities between treatment groups, with baseline bacteraemia identified as a factor of greater importance in the tigecycline treatment group (Fig. 2). A review of baseline bacteraemia by indication revealed similar incidences of death between treatment groups in patients with baseline bacteraemia in all infection types, except for patients in the VAP subgroup of the HAP trial (Table 2). In the approved indications, 5.1% of tigecycline-treated and 5.8% of comparator-treated patients with baseline bacteraemia died.

Persistent bacteraemia, defined as blood cultures positive after 24 h of therapy, was more common in tigecycline-treated patients [8]. Overall, 25 tigecycline-treated patients and 9 comparator-treated patients had persistent bacteraemia; persistent bacteraemia in the approved indications occurred in 6 patients treated with tigecycline (24.0%) and 3 patients treated with comparator (33.3%). Among patients with baseline bacteraemia who subsequently died, 9 tigecycline-treated patients (32.1%) and 1 comparator-treated patient (6.7%) also had persistent bacteraemia; none of these patients were receiving tigecycline for an approved indication. Moreover, 7 (50.0%) of 14 HAP patients treated with tigecycline and 2 (28.6%) of 7 RP 307 patients treated with tigecycline

Table 2
Mortality in patients with baseline bacteraemia by infection type in the modified intention-to-treat population.[a]

	Tigecycline [*n* (%)][b]	Comparator [*n* (%)][b]
Approved indications		
cSSSI	2/28 (7.1)	1/31 (3.2)
cIAI	4/75 (5.3)	5/58 (8.6)
CAP	1/35 (2.9)	1/31 (3.2)
Non-approved indications		
HAP	14/44 (31.8)	6/42 (14.3)
Non-VAP	5/26 (19.2)	5/29 (17.2)
VAP	9/18 (50.0)	1/13 (7.7)
RP 307	7/25 (28.0)	2/9 (22.2)

cSSSI, complicated skin and skin-structure infection; cIAI, complicated intra-abdominal infection; CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; RP, resistant pathogen.

[a] No patients with baseline bacteraemia died in the diabetic foot infection study.
[b] Percentages are based on total number of patients with bacteraemia at baseline.

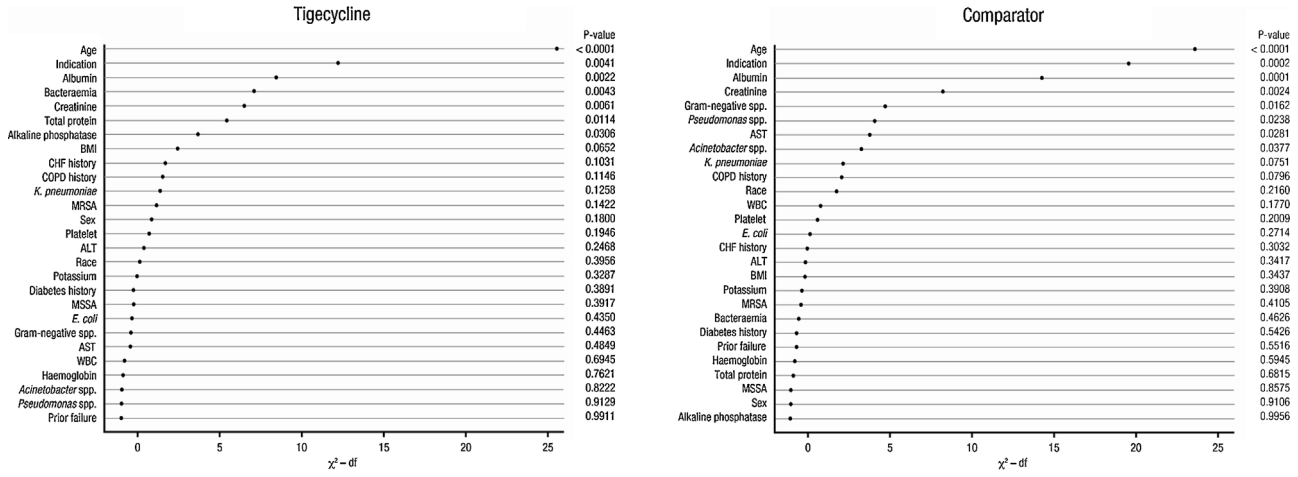

Fig. 2. Potential predictors of mortality based on logistic regression modelling based on 10 randomised trials (the 315 and 400 complicated intra-abdominal infection trials and the 900 complicated skin and skin-structure infection trial did not collect albumin levels and were not utilised in this analysis). Larger values imply greater importance. Sensitivity analyses including all 13 trials did not alter the potential predictors identified. Sensitivity analysis using the seven trials collecting Acute Physiology and Chronic Health Evaluation (APACHE) II score data identified this as a potential predictor both in tigecycline and comparator treatment groups. BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MRSA, meticillin-resistant *Staphylococcus aureus*; ALT, alanine aminotransferase; MSSA, meticillin-sensitive *S. aureus*; AST, aspartate aminotransferase; WBC, white blood cells.

with baseline bacteraemia who subsequently died also had persistent bacteraemia. Both of the RP 307 patients were treated with tigecycline for primary bacteraemia as opposed to secondary bacteraemia in the other clinical trials.

4. Discussion

Study-level and patient-level analyses of clinical trial data were initiated by the sponsor (Pfizer Inc) to understand better the all-cause mortality difference identified in the tigecycline clinical trial programme [1]. The risk difference did not appear to be the consequence of treatment of a particular infection type based on sensitivity analyses conducted to assess the influence of individual studies and infection types on the overall results; however, the HAP trial and the RP 307 trial accounted for 52% of all deaths, despite having contributed only 15% of patients to the pooled analysis.

Patient-level analyses identified several risk factors traditionally associated with higher mortality; however, baseline bacteraemia was an important risk factor only in the tigecycline treatment group. Analysis by indication demonstrated that baseline bacteraemia was important in the subgroup of patients with VAP but not in the approved indications, which is consistent with a previous analysis [8]. Persistence of bacteraemia owing to low tigecycline serum concentrations, higher bacterial load in HAP patients and primary bacteraemia, and/or insufficient dose (discussed below) mechanistically may explain the excess risk of death in the subset of tigecycline patients with baseline bacteraemia.

Importantly, baseline pathogen and treatment assignment did not emerge as a risk factor in the patient-level analyses, whereas infection type (or indication) was an important risk factor for mortality. This suggests that the association between treatment and mortality is weaker than the association with other factors such as infection type.

The area under the concentration–time curve (AUC)/MIC ratio is currently the best pharmacodynamic predictor of tigecycline efficacy [9,10]. Mean AUC and median-free AUC/MIC were decreased in patients with VAP relative to those without VAP [11]. It has been speculated that an insufficient dose of tigecycline and increasing pathogen MIC may have contributed to the lower efficacy and excess mortality observed in the VAP subgroup of the HAP trial. Data from a recent phase 2 HAP trial exploring higher doses of tigecycline lend support to this hypothesis but are not conclusive [12].

Although progression of infection occurred in many who died, an association between lack of clinical efficacy and mortality is difficult to conclude owing to composite endpoints used in registration trial designs. In addition, patients with the higher probability of dying (e.g. increased APACHE II score), at least in the approved indications, had similar clinical outcomes whether treated with tigecycline or comparator. This was not the case for patients with HAP, specifically VAP. Similar to the patient-level analyses, this suggests that other variables such as infection type are important and that there is a more complex explanation of mortality than simply a lack of efficacy.

The US Food and Drug Administration (FDA) presented their own analysis of the tigecycline mortality data [13]. The FDA results and conclusions are in general agreement with our own, including the timing of the deaths and the identification of bacteraemia in HAP, but not other indications. Increased cardiac events identified by the FDA and observed in our own analysis (not shown) appear to be a progression of underlying infection and/or co-morbidities. A recently completed tigecycline thorough QT study does not suggest a direct cardiac toxicity and supports both our conclusion and that of the FDA [13,14].

Despite the identification of an all-cause mortality difference, the post hoc meta-analyses of all-cause mortality data from the tigecycline clinical trials, including our own, must be considered exploratory and hypothesis-generating. First, all-cause mortality was not a pre-specified powered endpoint, and no risk window was specified a priori. Using a 30-day mortality window resulted in a non-significant risk difference but does not eliminate the importance of the all-cause mortality signal. In addition, use of the modified intention-to-treat safety population may not perfectly reflect drug effects, since patients in many cases received limited dosing.

Second, the study pooled all-cause mortality data from different infectious disease indications. Both study-level and patient-level analyses suggest clinical heterogeneity, which may impact the interpretation and generalisability of the results [15]. For example, excess risk of mortality by individual infection type may be more important. Third, antibiotics are expected to reduce or prevent complications of infectious diseases and therefore decrease attributable mortality, not all-cause mortality [16].

In conclusion, our analyses identified the all-cause mortality difference in the tigecycline clinical programme and this difference has been confirmed by other independent analyses. In general, the deaths appear related to worsening or complications of the infection or underlying co-morbidities. Study-level and patient-level analyses have identified that patients in the HAP trial, particularly those with VAP with baseline bacteraemia, were at a higher risk of clinical failure and mortality. Owing to the increase in antibiotic resistance worldwide and the relative lack of available treatment options [17], tigecycline remains an appropriate treatment option for its approved indications. Ultimately, the choice of antibiotics should include a benefit/risk assessment, with consideration of the individual patient's particular clinical situation.

Acknowledgments

Programming support was provided by Jeff Goodrich of Pfizer Inc. Editorial support with manuscript preparation and submission was provided by Paul Hassan, PhD, and Charlotte Kenreigh, PharmD, of UBC Scientific Solutions, and was funded by Pfizer Inc.

Funding: This work was supported by Pfizer Inc.

Competing interests: PCM, MW, AE-T, PB and RDM are employees of, and also holds stock in, Pfizer Inc, which manufactures and markets the drug tigecycline.

Ethical approval: Not required.

References

[1] McGovern P, Wible M, El-Tahtawy, Biswas P, Meyer D. Mortality imbalance in the tigecycline phase 3 and 4 clinical trials. Crit Care Med 2010;38(Suppl 12) [Abstract 302].

[2] Prasad P, Sun J, Danner RL, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. Clin Infect Dis 2012;54:1699–709.

[3] Tasina E, Haidich AB, Kokkali S, Arvanitidou M. Efficacy and safety of tigecycline for the treatment of infectious diseases: a meta-analysis. Lancet Infect Dis 2011;11:834–44.

[4] Vardakas KZ, Rafailidis PI, Falagas ME. Effectiveness and safety of tigecycline: focus on use for approved indications. Clin Infect Dis 2012;54: 1672–4.

[5] Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother 2011;66:1963–71.

[6] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

[7] Wyeth Pharmaceuticals Inc. Tygacil®(tigecycline) for injection for intravenous use. Highlights of prescribing information. Philadelphia, PA: Wyeth Pharmaceuticals Inc.; 2012. http://labeling.pfizer.com/ShowLabeling.aspx?id=491 [accessed 08.02.13].

[8] Gardiner D, Dukart G, Cooper A, Babinchak T. Safety and efficacy of intravenous tigecycline in subjects with secondary bacteremia: pooled results from 8 phase III clinical trials. Clin Infect Dis 2010;50:229–38.

[9] Meagher AK, Passarell JA, Cirincione BB, Van Wart SA, Liolios K, Babinchak T, et al. Exposure–response analyses of tigecycline efficacy in patients with complicated skin and skin-structure infections. Antimicrob Agents Chemother 2007;51:1939–45.

[10] Bhavnani SM, Rubino CM, Ambrose PG, Babinchak TJ, Korth-Bradley JM, Drusano GL. Impact of different factors on the probability of clinical response in tigecycline-treated patients with intra-abdominal infections. Antimicrob Agents Chemother 2010;54:1207–12.

[11] Freire AT, Melnyk V, Kim MJ, Datsenko O, Dzyublik O, Glumcher F, et al. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. Diagn Microbiol Infect Dis 2010;68: 140–51.

[12] Ramirez J, Dartois N, Gandjini H, Yan JL, Korth-Bradley J, McGovern PC. A Randomized phase 2 trial to evaluate the clinical efficacy of two high-dosage tigecycline regimens versus imipenem/cilastatin for treatment of hospital-acquired pneumonia. Antimicrob Agents Chemother. 2013 [Epub ahead of print].

[13] Iarikov D, Alexander J, Charles J, Tracy L, Nambiar S. Analysis of an increase in all-cause mortality in tigecycline treated patients. In: 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). Washington, DC: ASM Press; 2011 [Abstract K-1428].

[14] Korth-Bradley JM, McGovern PC, Salageanu J, Matschke K, Plotka A, Pawlak S. Tigecycline does not prolong corrected QT intervals in healthy subjects. Antimicrob Agents Chemother. 2013.[Epub ahead of print].

[15] Thompson SG. Why sources of heterogeneity in meta-analysis should be investigated. BMJ 1994;309:1351–5.

[16] Wenzel RP. Perspective: attributable mortality—the promise of better antimicrobial therapy. J Infect Dis 1998;178:917–9.

[17] Infectious Diseases Society of America. The 10 × '20 Initiative: pursuing a global commitment to develop 10 new antibacterial drugs by 2020. Clin Infect Dis 2010;50:1081–3.