The Brazilian Journal of
INFECTIOUS DISEASES

www.elsevier.com/locate/bjid

ELSEVIER

Letter to the Editor

A comparative analysis between survivors and nonsurvivors patients treated with tigecycline

Dear Editor,

The US Food and Drug Administration (FDA) have issued a warning describing increased mortality risk associated with the use of tigecycline when compared to other drugs in the treatment of serious infections. Such increased risk was determined using a pooled analysis of randomized clinical trials which involved predominantly patients treated for ventilator-associated pneumonia (VAP).[1]

In the present observational and retrospective study, we determined the mortality predictor factors between survivors and nonsurvivors patients treated with tigecycline. Patients were enrolled in the study at 23 Latin American centers between February 2006 and June 2009. Data collection from clinical records was done using an electronic form (LatinUser® website; http://www.clinicalrec.com.ar). Two tailed hypothesis testing for difference in proportions and multivariable logistic regression to identify predictors of mortality were used for analysis.

Of the 301 eligible patients, 208 patients were male and the mean age was 49.7 (range 18–86). The overall in-hospital mortality was 36.5% (110/301 nonsurvivors vs 191/301 survivors). Univariate analysis showed that age, hospitalization in intensive care unit, APACHE II score, VAP, microbiological documentation, previous use of carbapenems and, immunocompromise were significantly associated with mortality. The multivariate analysis showed that only age [odds ratio (OR): 1.026; [95% CI 1–1.05], $p = 0.0202$]; VAP (OR: 2.757; [95% CI 1.13–6.69], $p = 0.0255$) and APACHE II score (OR: 1.228; [95% CI 1.10–1.23], $p = 0.0000$) were identified as independent risk factors for mortality (Table 1).

In concordance with the FDA warning, our study shows that in-hospital mortality with tigecycline was significantly higher in critically ill patients with VAP. Undoubtedly, from a strictly scientific point of view, there is no evidence to support tigecycline use in these patients. In that sense, Freire et al. reported significantly lower cure rates in clinically evaluable patients with VAP treated with tigecycline (47.9%) when compared to imipenem (70.1%) (−22.2% [95% CI lower limit, −39.5%]). Based on these results, tigecycline has not been approved by the FDA for the treatment of VAP.[2]

Considering the attainable extracellular epithelial lining fluid concentrations of tigecycline (0.37 μg/mL), the current dosage of 50 mg of tigecycline twice daily is probably underdosed for the treatment of VAP caused by typical, extracellular-acting bacteria such as *Acinetobacter* spp ($MIC_{90} \sim 1$ μg/mL).[3]

Regardless of these issues, the tigecycline pharmacological and microbiological profiles encourage physicians to use the drug for VAP due to multidrug-resistant (MDR)-pathogens. In that respect, we have published that more than 50% of the tigecycline prescriptions in Argentina were for VAP, mainly due to MDR-*Acinetobacter* spp.[4] This practice is justified by the high regional resistance rates of MDR-pathogens with limited therapeutic options (e.g. carbapenem-resistant *Acinetobacter* spp.; KPC-producing Enterobacteriaceae).

We know that clinical trials are indispensable tools to generate new knowledge and to test therapeutic options for the care mainly of critically ill patients, however, the epidemiological situation usually force physicians to incorporate the off-label use of some antibiotics as part of their daily practice (e.g. polymyxins, fosfomycin, sulbactam and other antibiotics, alone or in combinations).

In the specific case of tigecycline it is mandatory to conduct clinical trials to generate comparative evidence about tigecycline efficacy and safety in VAP using higher doses (i.e. 200 mg initial and 100-q12), as well as to determine the role of tigecycline combinations with other antibiotics (carbapenems, polymyxins, and fosfomycin among others).

Observational studies although helpful, are generally not adequate to address these issues, and controlled clinical trials will be necessary to provide sufficient and reliable evidence to support approval for new tigecycline indications and dosing schedules. Nevertheless, this process usually takes several years.

For the treatment of serious or life-threatening illness, FDA regulations, issued in 1992, allow for "accelerated approval" of a drug or biologic product that provides a "meaningful

Table 1 – Multivariate analysis of factors associated with mortality in patients treated with tigecycline.				
	Survivors (n = 191)	Non-survivors (n = 110)	p	OR
Age (mean)	47.31 SD 18.6 (18–86)	52.22 SD 21.4 (18–85)	0.0202	1.026 (95% CI, 1–1.05)
VAP (n; %)	98 (51)	74 (67)	0.0255	2.757 (95% CI, 1.13–6.69)
APACHE II (median)	11.45 SD 8.45 (0–27)	23.956 SD 13.1 (0–55)	0.0000	1.228 (95% CI, 1.10–1.23)
VAP, ventilator associated pneumonia.				

therapeutic benefit. over existing treatments".[5] Assuming the serious infections due to MDR-pathogens as a considerable unmet medical need, this type of programs may help to get new scientific evidence of tigecycline in a shorter time in order to improve our patients' clinical outcome.

Conflict of interest

The author is a speaker for Pfizer Argentina (formerly Wyeth SA).

REFERENCES

1. FDA Drug Safety Communication. Increased risk of death with Tygacil (tigecycline) compared to other antibiotics used to treat similar infections; 2010. http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm Sep (August 2011 date last accessed).
2. Freire AT, Melnyk V, Kim MJ, et al. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. Diagn Microbiol Infect Dis. 2010;68:140–51.
3. Burkhardt O, Rauch K, Kaever V, Hadem J, Kielstein JT, Welte T. Tigecycline possibly underdosed for the treatment of pneumonia: a pharmacokinetic viewpoint. Int J Antimicrob Agents. 2009;34:101–2.
4. Curcio D, Fernández F, Cané A, Barcelona L, Stamboulian D. Indications of a new antibiotic in clinical practice: results of the tigecycline initial use registry. Braz J Infect Dis. 2008;12:198–201.
5. FDA. Fast track and priority review programs; 2008. http://www.nationalaglawcenter.org/assets/crs/RS22814.pdf Feb (August 2011 date last accessed).

Daniel Curcio*
Hospital Municipal Chivilcoy, Infectología Institucional SRL, Buenos Aires, Argentina

* Correspondence address. Santo Tomé 52394-22 (1419), Buenos Aires, Argentina.
E-mail address: djcurcio@gmail.com

http://dx.doi.org/10.1016/j.bjid.2012.08.027