Effectiveness and Safety of Tigecycline: Focus on Use for Approved Indications

To the Editor—Since the US Food and Drug Administration (FDA) announced that tigecycline was associated with higher mortality than comparator antibiotics in an analysis of data from the available randomized controlled trials (RCTs) [1], 3 meta-analyses were published to “assess the effectiveness and safety of tigecycline” for the treatment of patients with infections [2–4]. Cai et al concluded that tigecycline had similar effectiveness but more adverse events than comparators and called for caution when tigecycline is used for the treatment of severe infections because of the possibility of increased mortality based on the FDA findings [2]. Yahav et al reported results similar to the FDA analysis, concluded that the increased mortality is attributed to tigecycline’s poorer effectiveness rather than fatal adverse events, and suggested that clinicians should avoid tigecycline monotherapy [3]. Finally, Tasina et al concluded that more research is required to clarify the role of tigecycline monotherapy in the view of increased mortality (which was not shown in their analysis) [4]. The differences in the results and conclusions of these meta-analyses can be explained, at least in part, by the different methodology (including statistical models and handling of undetermined outcomes), different number of included studies, and different data available or used in each analysis.

Tigecycline is currently approved in the United States for the treatment of patients with skin and soft tissue infections, complicated intra-abdominal infections, and community-acquired pneumonia. However, it is not approved for nosocomial pneumonia or diabetic foot infections. It is noteworthy that all 4 analyses discussed above (the 3 meta-analyses and the FDA analysis) [1–4] did not focus on patient populations for whom there is approval for use of tigecycline.

We analyzed and evaluated the data provided by these meta-analyses according to the indication for use of the antibiotic. Tigecycline was not associated with higher mortality than comparator antibiotics in patients with infections for which there is approval for its use (5268 patients, 11 trials; 2.5% tigecycline versus 1.8% comparator; odds ratio [OR], 1.38; 95% confidence interval [CI], 0.95–2.00; \( P = .09 \)) (Figure 1) [5–15]. Furthermore, tigecycline was as effective as comparators for the treatment of patients with infections that are approved indications for the use of the drug (clinically evaluable population, 4195 patients, 11 trials; OR, 0.96; 95% CI, 0.81–1.13; \( P = .60 \)) [5–15], but it was less effective for patients with infections that do not belong to the group of approved indications (clinically evaluable population, 1447 patients, 2 trials; OR, 0.67; 95% CI, 0.51–0.86; \( P = .002 \)) [16, 17]. We did not include the trial by Florescu et al [18] in our primary analyses because it studied patients with nosocomial pneumonia and primary bacteremia without providing specific data for mortality in these groups of patients. However, the inclusion of this trial in secondary analyses did not lead to statistically significant findings.

There is a discussion on whether data from unpublished RCTs should be included in a meta-analysis. In 3 of 4 meta-analyses mentioned above as well as in our analysis, unpublished data were used. We have shown that there are important discrepancies between data reported in conference abstracts and data reported in papers subsequently published in peer-reviewed journals [19, 20]. In keeping with this observation, Tasina et al report that there were differences between the unpublished trials and the FDA report regarding the number of reported deaths. When unpublished RCTs are included in a meta-analysis, their data cannot be used in sensitivity analyses owing to lack of significant information regarding the total quality of trials and/or several independent variables of quality, including concealment of allocation and double-blinding procedure.

In conclusion, an analysis of the evidence from RCTs comparing tigecycline with other antibiotics for patients with infections for which there is approval for use of the drug shows that tigecycline is not associated with statistically significant higher mortality than comparator antibiotics. Although the analysis shows a trend toward higher mortality with tigecycline therapy (\( P = .09 \)), no definite conclusions can be drawn from data that lack statistical significance. Some may think that this trend is of interest, especially because the addition of data from RCTs studying patients who received tigecycline for infections for which the drug is not approved makes the differences statistically significant. However, in an era of multidrug-resistant, extensively drug-resistant, and pan-drug-resistant bacterial infections and given the scarcity of new antibiotics, especially for gram-negative bacterial infections, it is probably prudent to support
the availability of tigecycline, bearing in mind its advantages and disadvantages. Considering that 3 registered trials that sought to further study the effectiveness and safety of tigecycline were terminated or suspended because of inability to enroll patients, it seems that an individual patient data meta-analysis would be helpful to reach safer conclusions on this important clinical issue.

**Note**

**Potential conflicts of interest.** M. E. F. has participated on the advisory boards of Astellas, Bayer, and Pfizer and has received lecture honoraria from Astellas, AstraZeneca, Cipla, Glenmark, Merck, Novartis, and Pfizer.

All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**Konstantinos Z. Vardakas,**<sup>12</sup> **Petros I. Rafaillidis,**<sup>1,2</sup> and **Matthew E. Falagas**<sup>1,2,3</sup>

<sup>1</sup>Alfa Institute of Biomedical Sciences, and  
<sup>2</sup>Department of Medicine, Henry Dunant Hospital, Athens, Greece; and  
<sup>3</sup>Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts

**References**


Correspondence • CID 2012;54 (1 June) • 1673

Figure 1. Mortality of patients with infections for which there is approval for use of tigecycline (meta-analysis of data from relevant clinical trials comparing the effectiveness and safety of tigecycline and other antibiotics). Abbreviations: CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.


Correspondence: Matthew E. Falagas, MD, MSc, DSc, Alfa Institute of Biomedical Sciences (AIBS), 9 Neapoleos St, 151 23 Marousi, Greece (m.falagas@aibs.gr).