Correspondence

Tigecycline and Bacteremia—The Dangers of Post Hoc Analysis of Pooled Data

To The Editor—It was with great interest that I read the article by Gardiner et al [1] on the safety and efficacy of intravenous tigecycline in secondary bacteremias. The authors are all employees of Pfizer, the company that manufactures tigecycline. Gardiner et al [1] performed a meta-analysis of 8 previously published trials by pooling the available data on secondary bacteremias [2–11]. This was an interesting idea, both because there have been no trials to determine whether tigecycline is effective in bacteremic patients and also given the theoretical concerns stemming from the low serum levels and its mostly bacteriostatic activity [12, 13]. One must recognize that the article mentions several of its own shortcomings: the fact that this is a post hoc analysis and that the patients were not enrolled for the treatment of bacteremia; the extreme heterogeneity in the studies’ design, which varied greatly in the type of infections and in the exclusion criteria; and its limited power to show a statistically significant difference, most notable in the subset analysis by organism.

All these issues render dubious the validity of the final statement: “Tigecycline demonstrated cure rates similar to comparator and appears safe and effective in subjects presenting with bacteremia secondary to [complicated intra-abdominal infection] cIAI, [complicated skin/skin-structure infection] cSSSI, and [community-acquired bacterial pneumonia] CAP” [1, p. 237] Similar wording is also used in the conclusions section of the abstract.

What is even more troubling is the quality of the data extrapolated from these studies. In many instances, the comparator antibiotic therapy was not the preferred regimen for treatment of the specific bacteremia based on the isolated pathogen. This would explain the low rate of cure in bacteremic patients—only 78.5% in the comparator group—despite the frequent exclusion of complicated cases, such as patients with chronic kidney disease or immunosuppression, among others. To elaborate on this point, methicillin-sensitive Staphylococcus aureus bacteremias were not treated with oxacillin, nafcillin, or cefazolin but with vancomycin, despite ample proof that vancomycin is not as effective in this scenario [14]. Particularly puzzling was the extremely low cure rate (68.4%) for Streptococcus pneumoniae bacteremias in the comparator group. Upon review of the original articles, it appears that most, if not all, of the cases were from the community-acquired pneumonia studies. The comparator drug in this case was levofloxacin. It was dosed exclusively at 500 mg once daily in one study, whereas in the other study the investigator could choose 500 mg either once daily or twice daily. The Infectious Diseases Society of America guidelines on community-acquired pneumonia state that the recommended dosage for levofloxacin is 750 mg daily [15], even in cases without concomitant bacteremia.

There are also concerns for the subset of patients with methicillin-resistant Staphylococcus aureus (MRSA), because none of the studies required monitoring of vancomycin levels. Therefore, some of the patients may have received subtherapeutic treatment.

It is quite possible that tigecycline is more effective in treating bacteremia than previously thought. Nevertheless, on the basis of the above elucidation, I disagree that it has been shown to be as effective as standard therapy.

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References

To the Editor—We appreciate the in-...