Correspondence

Imbalanced Mortality Evidence for Tigecycline: 2011, the Year of the Meta-analysis

To the Editor—During 2011, 3 high-quality meta-analyses investigated, among other clinical questions, the difference between mortality rates for any cause of 30-day mortality for tigecycline and any other antibiotic [1–3]. Although the meta-analyses of Cai et al [1] and Tasina et al [2] concluded that the evidence of mortality differences should be considered nonconclusive, Yahav et al [3] boldly concluded that the differences between mortality rates were statistically significant. Given that these meta-analyses included almost the same published studies, it is worth asking why they arrived at different conclusions regarding mortality differences.

The source of disagreement between authors is the statistical model they applied. Although the empirical evidence (ie, published studies) can be declared correct, the statistical model is always “wrong.” The statistical model is wrong in the sense of its limitations to describe the complexity of the problem at hand. How can we trust the conclusions of a wrong statistical model? A wrong statistical model upgrades to become useful if it is able to predict the published studies included in the systematic review. For example, in a recent publication [4] we pointed out that the model used by Yahav et al was not able to predict 6 of 14 studies, so a bold conclusion from this statistical model is definitively misleading.

Another way to interpret the evidence of mortality in these meta-analyses is by asking whether the extent of difference in mortality rates is related to the underlying risk of the patients in the different trials. If this relationship exists, then it has important implications in the interpretation of the mortality results (eg, by detecting which patients may be at risk under application of tigecycline and which patients may be not).

A natural way to measure underlying risk in a clinical trial is by estimating the mortality rate of the control group. We can assess the relationship between underlying risk and difference in mortality rates using the model proposed by Sharp and Thompson [5]. Figure 1 shows the regression line that summarizes this relationship for the tigecycline meta-analysis published by Yahav et al [3]. The negative slope of this line indicates a decrease in mortality differences as the mortality in the comparator group increases. Moreover, the predictive confidence bounds include all studies used in the meta-analysis, which gives confidence in the conclusions coming from this model.

The message of Figure 1 is that we cannot make a general statement about mortality differences for tigecycline; it may depend on the underlying mortality of the study population. For populations with low mortality rates (left hand side of Figure 1), the model favors the comparator drug, whereas for populations with increased mortality rates, there is no differences between the groups’ mortality rates.

We hope that our view will motivate readers to think more critically about meta-analysis results in general.

Notes

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Figure 1. Evidence of mortality in tigecycline compared with any other antibiotic. Each vertical line represents a study result. The points correspond to the observed odds ratio of mortality, and the dashed lines represent the 95% confidence intervals. The meta-regression line is presented by the solid line in the center with its 95% predictive interval.
Potential conflicts of interest. D. C. is an adviser of Pfizer (formerly Wyeth) Laboratories Argentina for antibiotics, and he has participated in several experimental and observational studies with tigecycline (Tygacil). P. E. V. certifies no potential conflicts of interest.

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