Reply to Tarchini

To the Editor—We appreciate the opportunity to respond to Dr. Tarchini regarding the important questions he poses in his letter. The following addresses each of his points in turn. First, as has been repeatedly demonstrated, achievement of vancomycin trough concentrations in the range of 15–20 mcg/mL does not necessarily result in improved outcomes (compared with lower trough concentrations). There have been several papers published showing just the opposite, similar, or worse clinical outcomes [1–3] with higher rates of nephrotoxicity associated with vancomycin trough concentrations 15 mcg/mL [1–6]. Importantly, this has been demonstrated using multivariate techniques to adjust for severity of illness and other risk factors [4, 5]. We performed a similar analysis using the data from the telavancin studies, wherein we examined outcome measures by vancomycin trough category (10 mcg/mL, 10–14 mcg/mL, and ≥15 mcg/mL) and found lower clinical response rate, higher mortality, and higher rates of nephrotoxicity in the highest trough group [7]. Importantly, Acute Physiology and Chronic Health Evaluation (APACHE) scores at baseline were also similar across the three patient groups, and the findings held up after adjusting for important covariates that would predict poor outcomes. These observations, along with the mortality reported in the vancomycin arm of the Assessment of Telavancin for Treatment of Hospital-Acquired Pneumonia trials, suggest that inadequate dosing of vancomycin in these studies is unlikely.

In addition, it is important to note that the support for the vancomycin trough concentration recommendations are graded as IIIB (moderate evidence for support and from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees), which is rather soft [8]. Unfortunately, there are no adequately controlled prospective studies to support the recommended trough concentrations.

Finally, the studies were conducted as registrational studies. In the recent FDA guidance on conduct of registrational trials, the following recommendation was made: “The active comparator should be an antibacterial drug at the recommended dosage that is FDA-approved for the treatment of ‘nosocomial pneumonia’” [9].

In response to Dr. Tarchini’s second question, there were only 20 patients (2.7% of 754 treated) who were switched from vancomycin to an antistaphylococcal penicillin (footnote Table 3, original report) [10]. Given that the efficacy and safety outcomes of this small cohort were similar to that of the entire vancomycin-treated group, their data were included with that of the larger population.

With regard to the third question, all but 19 of 92 patients with baseline blood cultures containing a respiratory pathogen had the same pathogen in respiratory cultures. Only 5 of these 19 patients were included in the microbiologically evaluable population. Identity between the two sources was based on genus, species, and antimicrobial susceptibility pattern. More sophisticated techniques to determine identity were not carried out, so it is possible that some of these patients had other sources for their bacteremia.

We sincerely hope that our responses reassure the readership of the validity and robustness of the telavancin clinical trial data.

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