Inferiority of Vancomycin Dosing and Design?

To the Editor—SOLO II (Oritavancin Versus IV Vancomycin for the Treatment of Patients With Acute Bacterial Skin and Skin Structure Infection) shows how difficult antimicrobial trials can be [1]. Not using more effective antibiotics than vancomycin, such as β-lactams, is a major problem. The choice of comparator in noninferiority trials is important as we cannot determine how effective the treatment is against an independent standard [2]. In SOLO II, it is uncertain whether the standard treatment arm did in fact receive adequate treatment. Indeed, in the Infectious Diseases Society of America guideline for treatment of methicillin-resistant Staphylococcus aureus (MRSA), avoiding vancomycin in methicillin-susceptible S. aureus is a performance measure [3]. Other than an inferior antibiotic for at least 30% and possibly 80% of the patients, vancomycin dosing was also poor, with approximately 50% not reaching adequate levels by 48 hours, assuming a vancomycin target of 10 µg/mL. It is clear from the reported data that this is a significantly skewed distribution; reporting the median and quartiles would be preferable. In addition, it is unclear whether blinding was maintained when adjusting vancomycin dosing. Were dummy doses also adjusted, and was a study of blinding adequacy considered?

If we are to truly compare antibiotics, trials should compare different strategies of protocolized antibiotic choices, not 1 antibiotic with a broad spectrum but inferior effectiveness to other standard drugs. Given the MRSA rates, vancomycin is reasonable as first-line treatment; however, receiving adequate clinical care requires that this is switched when microbiological information becomes available that allows use of a more efficacious antibiotic. Although this would add complexity and cost to the trial design, this cannot be accepted as an obstacle to an adequately resourced trial. SOLO II recruited 1019 patients across 29 sites over 29 months, despite 5 centers only contributing 10 patients in total [4]. It is unclear that including these centers adds greatly to the internal or external validity of this study, although clearly there were sufficient resources.

Finally, informed consent is required in clinical trials, stated in the Declaration of Helsinki [5]. Given the known inferiority of vancomycin compared to β-lactams, were patients informed they might be randomized to receive inferior treatment against guideline recommendations [3] vs the investigative treatment? If not, what comments did the research ethics committees make about this?

Note

Potential conflict of interest. Author certifies no potential conflicts of interest.

The author has 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.

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