Clinical Infectious Diseases

EDITORIAL COMMENTARY

A Collaborative Model for Endpoint Development: Advancing the Science of Antibacterial Drug Clinical Trials

Joseph G. Toerner and Edward Cox

Office of Antimicrobial Products, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland

(See the Major Article by Talbot et al on pages 603–7.)

Keywords. antibacterial drug development; non-inferiority trial design; clinical endpoints.

The development of new antibacterial drugs is challenging from both a scientific and economic perspective. Despite these challenges, there is a continued need for the development of new antibacterial drugs to address patient needs. While overcoming the many challenges that face antibacterial drug development will require a number of important issues to be addressed, establishing well-defined and reliable endpoints for use in clinical trials to evaluate new antibacterial drugs is an essential part of facilitating the development of new antibacterial drugs.

In this issue of *Clinical Infectious Diseases*, Talbot and colleagues provide an update from the Biomarkers Consortium of the Foundation for the National Institutes of Health (FNIH) describing their work on outcome assessments as endpoints for antibacterial drug clinical trials. The work of the FNIH Project Team is advancing the science of antibacterial drug clinical trials for evaluating treatments for acute bacterial skin and skin structure infections (ABSSSI), community-acquired bacterial pneumonia (CABP), and hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) by developing well-defined and reliable efficacy endpoints.

The FNIH Project Team's greatest impact has been on the development of a well-defined and reliable efficacy endpoint for ABSSSI. Their work led to an endpoint of reduction in lesion size by ≥20% at a 48- to 72-hour time point as an interim recommendation for use in ABSSSI trials. The magnitude of the treatment effect for this endpoint is supported by evidence derived from trials conducted during the time prior to antibacterial drug therapy becoming standard of care for most skin infections. As part of their endpoint development work, the FNIH Project Team evaluated the performance of this endpoint in previously conducted registrational trials.

Prior to establishing the interim endpoint recommendations for ABSSSI, there was significant uncertainty in this area of drug development that had a negative impact on the field. The FNIH Project Team addressed this uncertainty by providing a clear efficacy endpoint that facilitated antibacterial drug trial conduct. Three new drugs have been approved for treatment of ABSSSI that were evaluated using this new endpoint.

Some clinicians have criticized the new ABSSSI endpoint because the data that were relied upon to determine the treatment effect are from trials conducted several decades ago [1]. In contrast, other clinicians have embraced the new ABSSSI endpoint as a highly relevant time point in the clinical assessment of the patient [2], and supported the importance of the early endpoint in concert with the traditional timing of the "test of cure" outcome assessments [3–5].

The FNIH Project Team's new research efforts in the development of a patient-reported outcomes measure (PRO) for ABSSSI provide information from the patient's perspective. Summary results of their ongoing qualitative work describe the main themes from patients about their illness. For example, the concept elicitation interviews found that patients with ABSSSI were concerned about the enlargement and swelling of the ABSSSI lesion. This information supports that a primary efficacy endpoint of ≥20% in the size of the ABSSSI lesion at 48–72 hours is important to patients and suggests that the "patient voice" is potentially included in this primary efficacy endpoint. Furthermore, the earlier timing of endpoint assessment should minimize losses to follow-up and thereby reduce missing data in a clinical trial.

The additional developmental work that the FNIH Project Team plans on a PRO for ABSSSI will provide a more complete clinical evaluation, including information at a later visit following completion of antibacterial drug therapy. Although a new PRO may not be an appropriate primary efficacy endpoint for a noninferiority trial (because the data may not exist for determining a treatment effect for an active comparator antibacterial drug for the PRO assessment), it nevertheless provides

Received 13 November 2015; accepted 18 November 2015; published online 13 December 2015.

Correspondence: E. Cox, Office of Antimicrobial Products, FDA/OMPT/CDER/Office of New Drugs, White Oak Building #22, Rm 6212, 10903 New Hampshire Ave, Silver Spring, MD 20993 (edward.cox@fda.hhs.gov).

Clinical Infectious Diseases® 2016;62(5):608–9

 DOI: 10.1093/cid/civ1007

a means to capture important information from the patient's perspective during the treatment course and recovery from ABSSSI.

The FNIH Project Team's work on CABP has provided valuable input on clinical outcome assessments and trial designs. In comparison to ABSSSI, the level of drug development for CABP has been less. However, sponsors that are interested in developing an antibacterial drug for CABP can be reassured that improvement in at least 2 of the 4 symptoms of CABP (chest pain, frequency or severity of cough, amount of sputum production, and difficulty breathing) with no worsening of the other symptoms at day 3 to day 5 will be accepted by the US Food and Drug Administration as a primary efficacy endpoint in CABP clinical trials. The continued work of the FNIH Project Team on a well-defined and reliable PRO as a primary efficacy endpoint for CABP should help to further refine this endpoint and its evaluation.

Based upon review of previously conducted studies, there is a robust treatment effect for the outcome of all-cause mortality in HABP/VABP. Although patients with HABP/VABP often have multiple comorbidities that contribute to fatal outcomes, the additional mortality observed in patients who were not treated with effective antibacterial drugs demonstrates the important effect of antibacterial drugs in reducing mortality in HABP/VABP. Noninferiority trial designs using an all-cause mortality endpoint can establish a clear finding of efficacy for a new antibacterial drug. Nonetheless, there is a desire to evaluate endpoints other than all-cause mortality. We concur that capturing other potential endpoints in a HABP/VABP trial can enhance the ability to clearly describe the overall benefit for patients. We look forward to the FNIH Project Team's continued work in HABP/VABP that will further evaluate the patient's perspective and provide additional understanding of patient outcomes and efficacy endpoints.

We recognize the important work of the FNIH Project Team in developing endpoints for ABSSSI, CABP, and HABP/VABP clinical trials. The advances in ABSSSI endpoints generated by the FNIH Project Team's work have had a strong impact on drug development in this area, and we are optimistic that advances in endpoint development for CABP and HABP/VABP trials will also address one important component among several that are needed to stimulate interest in new antibacterial drug development in these areas. We look forward to the continued work of the FNIH Project Team in advancing endpoint development.

Notes

Disclaimer. The opinions in this editorial are those of the authors and do not necessarily represent the views of the US Food and Drug Administration.

Potential conflict of interest. The authors are regarded as nonvoting members of the Project Team of the Biomarkers Consortium of the Foundation for the National Institutes of Health and participate in discussions during the face-to-face meetings and teleconference calls. Both 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.

References

1. Drusano G. Early endpoints for acute bacterial skin and skin structure infections. Antimicrob Agents Chemother **2012**; 56:2221–2.
2. Itani KM, Shorr AF. FDA guidance for ABSSSI trials: implications for conducting and interpreting clinical trials. Clin Infect Dis **2014**; 58(suppl 1):S4–9.
3. Boucher HW, Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW. Once-weekly dalbavancin versus daily conventional therapy for skin infection. N Engl J Med **2014**; 370:2169–79.
4. Corey RG, Good S, Jiang H, et al. Single-dose oritavancin versus 7–10 days of vancomycin in the treatment of gram-positive acute bacterial skin and skin structure infections: the SOLO II noninferiority study. Clin Infect Dis **2015**; 60:254–62.
5. Shorr AF, Lodise TP, Corey RG, et al. Analysis of the phase 3 ESTABLISH trials of tedizolid versus linezolid in acute bacterial skin and skin structure infections. Antimicrob Agents Chemother **2015**; 59: 864–71.