End Points in Hospital-Acquired Pneumonia and/or Ventilator-Associated Pneumonia Clinical Trials: Food and Drug Administration Perspective

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Identification of reliable, reproducible, and precise end points for future studies of hospital-acquired and ventilator-associated pneumonia is of paramount importance for approval of new therapeutic agents. As required by the Code of Federal Regulations 21 CFR 314.126, the methods of assessment of a subject’s response (ie, end points) must be well defined and reliable. The study protocol and results should explain the variables measured, the methods of observation, and criteria used to assess response. Meeting these requirements has proven to be problematic in clinical trials for the evaluation of new products for the treatment of hospital-acquired and ventilator-associated pneumonia because of the subjectivity of assessing a clinical response end point. There are multiple issues and caveats to consider when selecting appropriate end points for these trials.

Nosocomial pneumonia is the second most common hospital-acquired infection after urinary tract infection [1]. Reported mortality rates range from 38% to >70%, and are particularly high in the subset of patients with ventilator-associated pneumonia (VAP) [2]. The selective pressure of antimicrobial use has resulted in a shift in the epidemiology of causative pathogens and increased the likelihood of multidrug-resistant organisms [3]. For these and other reasons, safe and effective new antibacterial agents are needed, but development of these therapies must be performed using clinical trial designs that permit interpretation of results. This article discusses various outcome measures to consider for use in clinical trials of products for hospital-acquired pneumonia (HAP) and/or VAP.

END POINTS FROM PREVIOUS TRIALS OF HAP AND/OR VAP

As discussed in a 1998 draft guidance for industry published by the US Food and Drug Administration [4], the primary end point for HAP and VAP trials was clinical cure. Clinical cure was defined as a complete resolution of all signs and symptoms of pneumonia, with improvement or lack of progression of all abnormalities on chest radiograph by the 7–21-day test-of-cure visit. Clinical outcome is a composite end point that relies on an investigator’s subjective assessment. The use of this end point is somewhat limited by the fact that the disease entity is difficult to accurately define and diagnose, and therefore, the ability to describe resolution is also difficult. An important secondary outcome discussed by the guidance was microbiologic outcome, stratified into 8 categories: eradication, presumed eradication, persistence, presumed persistence, superinfection, recurrence, new infection, and colonization. Analysis populations were not defined in the guidance.

REVIEW OF END POINTS FROM RECENT REGISTRATIONAL TRIALS

Five antibacterial drugs are approved for the treatment of either nosocomial pneumonia or lower respiratory tract infection; these drugs include ciprofloxa-
acín, levofloxacin, piperacillin-tazobactam, ceftazidime, and linezolid. As discussed elsewhere in this supplement [5], most recent drug-development programs have used end points that were reasonably similar to those described in the draft guidance (ie, the investigator assessment of clinical response at the test-of-cure visit for the clinically evaluable and the microbiological intent-to-treat populations. The clinically evaluable, also known as per-protocol, population usually consists of patients who meet the definition for the intent-to-treat population (all patients who were randomized) and who follow important components of the trial as specified in the protocol. The microbiological intent-to-treat population includes all randomized patients who have a baseline bacterial pathogen known to cause HAP and/or VAP against which the test drug has activity.

The definition of cure is as described above, and clinical failure was defined as a lack of response, relapse, or death (usually attributable, although all-cause was occasionally used). A third outcome category was that of indeterminate, if the outcome could not be determined. Older registrational trials may have used analysis populations other than the clinically evaluable or microbiological intent-to-treat populations.

Secondary end points included clinical response by baseline isolate for patients in the microbiologically evaluable population. A simplified microbiologic response outcome consisted of eradication, persistence, or indeterminate. Some sponsors also evaluated all-cause mortality and time to resolution of fever. Use of other time-to-event end points and various scoring systems varied among applications, likely because most of the products were approved many years ago.

**HISTORICAL EVIDENCE OF TREATMENT EFFECT**

Sorbello et al [6] conducted a review of the historical literature to establish the treatment effect of antibacterial therapy, compared with placebo, for nosocomial pneumonia. Thirty-nine published articles were identified, but none described placebo-controlled or dose-ranging studies. The end point evaluated in these studies was all-cause mortality. Of these studies, 12 were nonrandomized, observational studies evaluating all-cause mortality with use of a placebo substitute of inadequate, inappropriate, or delayed initial therapy. Use of these data to indirectly derive a placebo all-cause mortality rate estimate of 62% seems to be reasonable, because inadequate and/or inappropriate or delayed initial therapy is likely no worse than actual placebo. Nine active controlled, randomized, prospective efficacy studies were used to establish the active control all-cause mortality rate estimate of 20%. Very limited to no placebo-controlled literature on clinical response or other nonmortality-related end points was discovered during the literature review.

**END POINTS FOR FUTURE TRIALS**

Although many different end points have been suggested as clinically relevant and important to health care providers and patients, the problem remains that there are few data other than those for all-cause mortality to establish the treatment effect of antibacterial therapy. Certainly, these end points may be used in a superiority trial or as secondary end points in noninferiority trials. Such end points include clinical response, time to event (eg, hospital discharge, extubation, normalization of temperature and white blood cell count, oxygen saturation, respiratory rate, and pulse), radiologic and microbiologic outcome, and change in Clinical Pulmonary Infection Score or other scoring systems [7, 8]. However, none of these have been validated as surrogate markers, nor has any correlation between them and either clinical response or all-cause mortality been evaluated in prior registrational trials.

A related issue is the timing of assessment of end points, which likely will depend on the end point that is selected. Options include at the end of treatment, during the course of treatment to evaluate improvement, at the test-of-cure visit, or at the first time of determination of clinical failure (48–72 h after initiation of therapy). Of the 23 studies used in the analysis by Sorbello et al [6], more than half did not specify when the mortality end point was assessed, and a few used 28–32 days as the time of assessment.

For a mortality end point, there are some issues to consider. Mortality, although not difficult to define, is not a clean end point, because determining attributability is in the eye of the beholder and may be unclear even when an autopsy is performed. All-cause mortality may be related to underlying comorbidities and gives a false impression that, somehow, the antibacterial treatment is related to the deaths. Another question pertains to the amount of the treatment effect of antibacterial therapy on a given end point that is reasonable to health care providers and patients to sacrifice when selecting a noninferiority margin. Preserving more of the effect is desirable for an end point, such as mortality; however, sample sizes may become quite large with very small margins.

**SUMMARY**

As discussed above and elsewhere in this supplement, the majority of the data for the historical evidence of treatment effect in HAP and/or VAP is for all-cause mortality, although indirectly derived. For other end points to be used as primary in noninferiority trials, the historical evidence of treatment effect, compared with placebo, must be established for the study results to be interpretable and fulfill the requirements of the Code of Federal Regulations. Sound scientific data and justification must be the rationale for the final design of trials for these significant and common infections.
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