Understanding Early and Late Endpoints in Registrational Trials of Community-acquired Bacterial Pneumonia

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(See the Major Article by Bart et al on pages e2607–12.)

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“It’s tough to make predictions, especially about the future.”

Does this humorous aphorism (perhaps erroneously attributed to baseball great Yogi Berra [1]) apply to the early clinical response (ECR) endpoint promulgated by the US Food and Drug Administration (FDA) in 2014 for use in trials of investigational antibiotics for the treatment of community-acquired bacterial pneumonia (CABP) [2]? The answer is “Apparently not.... mostly.” Please read on for an explanation.

The FDA laudably undertook an evaluation of the primary endpoint that it requires per the 2014 CABP Guidance document [3]. As reported by Bart et al in this issue of *Clinical Infectious Diseases*, the Agency’s analysis of patient-level data from 6 recent registrational CABP trials demonstrated that the concordance between outcomes for the “new” ECR endpoint (assessed at days 3–5 of treatment) and the “traditional” test-of-cure

late endpoint (assessed after completion of treatment) was good—85.6%. Furthermore, ECR success was highly predictive of late endpoint success, with a positive-predictive value of 92.9%. However, Mr Berra was correct as far as the predictive performance of ECR failure: the negative-predictive value of ECR failure was quite low (46.2%). So, early failure did not reliably predict late failure. (Note: Good news for patients!) The rate of ECR successes that ultimately failed and ECR nonresponders that ultimately succeeded was 6.0% versus 8.4%, respectively.

Readers may wonder how it would be possible for the FDA to perform these analyses if both the ECR endpoint and the late endpoint were assessed in real time by the investigator, as is commonly done for the latter. In fact, the assessment methodology for the 2 endpoints differs substantially. In contrast to the assessment of the test-of-cure outcome, the ECR outcome is determined programmatically (and post hoc) by analysis of the daily evolution of the presence and severity of CABP symptoms. Hence, the 2 endpoints are determined independently, allowing for the analyses performed.

The reader may also ask why the FDA thought it necessary to change the CABP primary endpoint (both timing and individual components) from a late endpoint to an early endpoint, especially when

European regulatory authorities continue to require the late endpoint, as Bart et al acknowledge. The answer is not entirely obvious absent an understanding of the history of the FDA’s recent endpoint journey [4], which commenced in 2010 when the Agency issued new guidance on noninferiority (NI) trials that reflected their conclusion that—since some infections improve over time even without antibiotic treatment—an ineffective antibiotic might achieve “success” in an NI trial [5].

The FDA subsequently determined that for CABP—and also for acute bacterial skin and skin structure infection (ABSSSI)—the greatest antibiotic treatment effect occurred during the first few days of treatment [2, 6]. These data allowed the FDA to calculate an NI “margin” (ie, the acceptable difference in efficacy between the test antibiotic and the active control) for each indication. The ability to justify rigorously an NI margin is the sine qua non of an NI trial design. Furthermore, the ECR endpoint was considered an improvement over the traditional late endpoints because the early data points are objective, measurable, reproducible, and verifiable. In addition, they more closely capture how a patient “feels and functions.”

A number of very rational objections to the use of the ECR endpoint have been raised; these points have been summarized previously [4]. A particularly

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important consideration is that, during review of a New Drug Application, the FDA does not ignore longer-term outcome data, but rather evaluates patient outcome at the post-treatment, test-of-cure evaluation; serious side effects or poor efficacy at late follow-up would raise concerns about approvability. Other potential objections to the ECR endpoint must be viewed in the context of the Agency's overriding need for a rigorous NI design justification in the registrational trial setting [7–9]. Although use of a superiority design overcomes many of the challenges of an NI design, this approach is often infeasible in the setting of acute, severe infection [10].

Returning to the article at hand, the conclusions of Bart et al are consistent with those from analyses of recent individual trials (unsurprisingly, since they presumably form part of the FDA database). For example, in a pooled analysis of 2 solithromycin versus moxifloxacin phase 3 CABP trials, ECR success had a high positive-predictive value (94.8%) for late clinical success at 5–10 days following treatment [11]. In a subsequent omadacycline versus moxifloxacin CABP trial, Ramirez et al [12] also observed a high positive-predictive value (>90%) of ECR success for late success. Other such examples can be found. These results parallel data for the ECR endpoint assessed in ABSSSI trials [13–16].

But what else can be learned from the Bart et al article? The authors' multivariate analyses of the association of baseline patient characteristics with the occurrence of late treatment failure in the context of ECR success provide important insights. Specifically, prior antibacterial drug therapy, *Chlamydomphila pneumoniae* or *Staphylococcus aureus* infection (especially *S. aureus* bacteremia), and severe chest pain were baseline characteristics associated with late failure. On the contrary, obesity was associated with late endpoint success among early endpoint responders.

The authors offer plausible explanations for these associations. For example,

it is known from a prior CABP program that prior effective antibiotic therapy can temporarily produce a salutary clinical response despite use of an ineffective investigational treatment [17]. Bart et al's analysis suggest an apparently favorable—and misleading—effect of prior antibiotic therapy at the ECR endpoint, even though such use was generally restricted to 1 dose of a short-acting antibacterial agent in the 72 hours prior to randomization. Relying only on an ECR endpoint in such patients would have missed an important observation; one potential interpretation is that the allowable amount of prior effective antibiotic therapy should be reduced further or even eliminated.

It is not surprising that *S. aureus* bacteremia present at trial entry was associated with late failure; investigators may have discontinued such patients from drug therapy even if improving and classified them as a failure simply because the agent studied was not highly active against methicillin-resistant *S. aureus* or because the protocol-dictated duration of treatment was too short for bacteremic *S. aureus* disease. Similarly, a given investigational agent (often a cephalosporin or glycopeptide) may have lacked activity against *C. pneumoniae*; persisting *C. pneumoniae* in patients who had mixed “typical” and atypical infection at baseline could result in late failure after initial improvement due to the study drug's activity against susceptible typical pathogens. Finally, the presence of severe chest pain at baseline could reasonably predispose investigators to discontinue therapy if chest pain persisted for more than the first few days of treatment. In future CABP trials, each of these factors should be evaluated in stratified subanalyses. In clinical practice, these observations may prove useful in the care of patients with CABP.

Another set of important observations related to mortality rates. The death rate in these 6 studies was substantially lower than would be expected for each Pneumonia Outcomes Research Team

(PORT) class. Selection bias for enrollment could have played a role (the PORT score for an individual is highly influenced by older age; less ill, but older patients might have been preferentially enrolled). Alternatively, protocol-driven patient care could have improved outcomes. Regardless, the data effectively put to rest the feasibility of using all-cause mortality as an endpoint in CABP trials.

In conclusion, Bart et al are to be commended for undertaking these analyses, which strengthen and extend the findings from analysis of individual trial databases. They are also to be commended for publishing the findings. These unique datasets held by the FDA could well be used to inform additional unresolved issues in design and execution of anti-infective registrational trials.

Notes

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