FDA Revisits Community-Acquired Pneumonia

By David Shlaes — July 9, 2020

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The FDA just published an [article][1] examining the relationship between their early clinical response endpoint for community-acquired bacterial pneumonia as compared to the late endpoint of cure at test of cure currently required by the European regulators. Accompanying this article is an [editorial][2] by George Talbot who provides an analysis of the data and, more importantly, some historical background for the study.

[1]: https://www.acsh.org
[2]: https://www.acsh.org
For those of us who lived through the nightmare of the FDA struggles with non-inferiority trial design throughout the years 2000-2012, reading the FDA study may be difficult. During those years, the FDA struggled with how to justify the so-called statistical margins used in clinical trials of antibiotics. The FDA wanted to be sure that the antibiotic effect was not similar to placebo, the statistical assumption that underlies all non-inferiority studies. They were also justifiably worried about the effect of prior, no-study antibiotics on the ultimate clinical outcome. This worry was clearly raised during a trial of daptomycin where the drug was inactivated by lung surfactant, yet appeared to work in a late-stage trial. That false sense of success was laid at the feet of short-term antibiotic therapy given prior to enrollment in the trial. These considerations led to a complete reconsideration of trial design for antibiotics in the treatment of bacterial pneumonia.

The FDA’s re-analysis showed essentially what we already knew. There is a huge antibiotic effect in the treatment of bacterial pneumonia. The effect is the greatest when looking at the early response to antibiotic therapy but is still large even when looking at later cure. In this case, the treatment effect for the early timepoint seemed to vary among different studies from 30 to 77%. The FDA decided that designating 20% as a conservative treatment effect would be OK after discounting for the fact that all these studies took place 80 years ago or more. These considerations ultimately led to a 12.% non-inferiority margin for studies of community-acquired bacterial pneumonia.

To summarize, the FDA paper, that analyzes data from six recent trials, clearly shows that the early response endpoints, *improvement in at least two of four specific symptoms (chest pain, cough, sputum production, and dyspnea) without any symptom worsening,* and clinical cure (the late endpoint) agreed (success or failure) 86% of the time. That this would be true was predicted by the careful studies of the FNIH team lead by Talbot in 2011 and the FDA’s analysis documented in the guidance [3] of 2014. A detailed look at the data reveals that discordant results may be explained. Early responders who had late failures were more likely to have severe chest pain on enrollment, an infection caused by *Staphylococcus aureus* or *Chlamydophila pneumoniae,* or to have received prior non-study antibiotic therapy.

Both FDA and Europe have already recognized the potentially confounding effect of prior non-study antibiotics in these trials. Both agencies also recognize that a total prohibition of prior antibiotic use would render trials infeasible. So both, pragmatically, limit the number of patients and the doses and types of prior antibiotics that are allowed.

The FDA concludes that the data they published provide an opportunity to reach international convergence on clinical trial design for the study of antibiotics in community-acquired bacterial pneumonia. I presume that they would like Europe to adapt the current FDA designation of early endpoints as definitive. But the data could also justify the FDA accepting clinical cure as definitive. As a physician, personally, I would like to put the FDA’s perseveration behind me and go back to using cure at test of cure as the ultimate endpoint. The concordance shown between the two endpoints is a tempting reason to do so and would make the most sense (in my humble view) to both patients and providers. But I cannot help but feel that the FDA would not agree with me.
Talbot concludes that this kind of analysis is very useful both for physicians and regulators and he lauds the FDA for publishing the data. I cannot agree more.

I also need to recognize the role of George Talbot in leading us through the morass of the FDA’s trials and tribulations during those critical years so that we ended up in a place where we could once again pursue the development of antibiotics. I’m not sure how long we would have been in Neverland without his steadfast leadership and insight.


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