Clinical Trial Design for Mild-to-Moderate Community-Acquired Pneumonia—An Industry Perspective

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The use of noninferiority clinical trials is problematic unless one can establish the benefit of the active control versus no treatment. In community-acquired pneumonia, there are no placebo-controlled clinical trials establishing the benefit of antibiotic treatment, because the observed benefit of sulfapyridine and, subsequently, penicillin was established before the advent of randomized clinical studies. Historical data and observational cohort studies have established the marked decrease in mortality resulting from antimicrobial therapy; however, mortality is not a suitable end point for contemporary clinical trials for mild-to-moderate community-acquired pneumonia that is treated with oral antimicrobial drugs in ambulatory patients. There are historical clinical data that describe the timing of spontaneous recovery in patients with documented pneumonia caused by Streptococcus pneumoniae. In addition, there is one contemporary clinical trial that demonstrated superiority in clinical response of levofloxacin versus a cephalosporin regimen of ceftriaxone and/or cefuroxime for treatment of mild-to-moderate community-acquired pneumonia. Using either the historical data or the superiority study of levofloxacin, one can justify a noninferiority margin of 10% for the per-protocol population and 15% for the microbiologically evaluable population for future noninferiority clinical trials for mild-to-moderate community-acquired pneumonia.

The past 2 years have resulted in a dramatic reversal by the US Food and Drug Administration (FDA) in the acceptance of noninferiority clinical trials of antibacterial drugs. Despite the fact that noninferiority clinical trials are the basis for nearly all antibacterial drugs approved in the past 2 decades and that studies using a noninferiority design were explicitly recommended by the FDA in earlier published guidances [1], the nonapproval of New Drug Applications for acute exacerbation of chronic bronchitis in 2005 [2] and acute bacterial sinusitis in 2006 [2] is based on the FDA’s new assessment of the inability of noninferiority clinical trials to demonstrate efficacy of the investigational product. In October 2007, the FDA issued a new draft guidance on clinical trial design that focused on noninferiority studies to support approval of antibacterial drugs [3]. This guidance makes 2 points. First, it is “not possible” to define a noninferiority margin for active-controlled studies of acute bacterial sinusitis, acute exacerbation of chronic bronchitis, or acute otitis media. Second, it is difficult to determine noninferiority margins for other indications to “ensure there is adequate scientific rationale for the effect size of the active control and the proposed NI [noninferiority] margin” [4, p. 3]. The FDA noninferiority guidance refers sponsors to International Conference on Harmonisation (ICH) document E10 for further clarity on study design including noninferiority margins [3]. It is important to understand that ICH document E10 is a general guidance for industry and is not specific to antibacterial drugs used to treat acute infectious diseases. It is clear from document E10 that, for the demonstration of efficacy, superiority trials, either placebo controlled or
Table 1. Distribution of bacterial respiratory pathogens, according to pneumonia severity index (PSI) risk class.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>I (n = 976)</th>
<th>II (n = 674)</th>
<th>III (n = 272)</th>
<th>IV (n = 175)</th>
<th>V (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pathogens</td>
<td>944</td>
<td>656</td>
<td>250</td>
<td>131</td>
<td>29</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>154 (16)</td>
<td>111 (17)</td>
<td>57 (23)</td>
<td>24 (18)</td>
<td>7 (24)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>90 (10)</td>
<td>72 (11)</td>
<td>25 (10)</td>
<td>16 (12)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>98 (10)</td>
<td>51 (8)</td>
<td>17 (7)</td>
<td>12 (9)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>17 (2)</td>
<td>22 (3)</td>
<td>11 (4)</td>
<td>5 (4)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Other gram-positive pathogens</td>
<td>60 (6)</td>
<td>60 (9)</td>
<td>16 (6)</td>
<td>7 (5)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Other gram-negative pathogens</td>
<td>109 (12)</td>
<td>110 (17)</td>
<td>38 (15)</td>
<td>18 (14)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>270 (29)</td>
<td>108 (16)</td>
<td>32 (13)</td>
<td>20 (15)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>96 (10)</td>
<td>68 (10)</td>
<td>12 (5)</td>
<td>11 (8)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Legionella pneumoniae</td>
<td>50 (5)</td>
<td>54 (8)</td>
<td>12 (5)</td>
<td>11 (8)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of pathogens. Percentages are based on the total number of pathogens in each PSI risk class (n). Data are from [8].

trial for acute exacerbation of chronic bronchitis enrolled subjects for >2 years [6]. As difficult as patient enrollment has been at the site level, we have been sobered by the resistance to placebo-controlled trials among international ethics committees and ministries of health. These organizations, which function under the same ICH guidelines as the FDA, have a far different view of the need for superiority trials. The most common reason for rejection is the fact that placebo-controlled studies contradict established treatment guidelines for the infection being treated. In addition, some European countries, although they accept the rationale of establishing the definitive efficacy of a drug versus placebo, nevertheless find a study without an active control of no value and therefore unethical. This recent experience in infections less serious than community-acquired pneumonia (CAP) provides important evidence against pursuing placebo-controlled trials, even for mild-to-moderate CAP.

MILD-TO-MODERATE CAP

What is mild-to-moderate CAP? Although the workshop divided the discussion into mild-to-moderate CAP and more-severe CAP, there really is no good way to separate these 2 indications. There are few scientific data to suggest that the microbial etiology is significantly different. From a regulatory perspective, oral therapies are usually excluded from labeling for severe infections, although pharmacodynamic parameters would not support this distinction for drugs that are highly bioavailable. One needs only to look at clinical practice in other countries to realize that the use of parenteral versus oral therapy for non-intensive care unit patients has more to do with hospital reimbursement than with medical science. Also, although patient scoring systems, such as the pneumonia severity index (PSI), are predictive of overall mortality, they have more to do with age and comorbidities than the severity of the acute episode of CAP [7].

A recent, large clinical development program for an antibiotic that ultimately was not approved for marketing included 7 CAP trials conducted globally, which enrolled nearly 2200


Figure 3. Time to pyrexia termination among patients with community-acquired pneumonia (n = 550) who received sulfapyridine treatment (treated) or did not receive treatment (untreated) in South Africa, 1938. *Difference between groups is 55.6% (95% CI, 48.5%–62.7%). Adapted from [32].
patients [8]. All studies characterized subjects at baseline by PSI class. Two trials included only PSI classes I and II, with orally administered drugs given to ambulatory patients. Two trials involved only hospitalized patients initially given treatment with intravenous therapy, and the other trials were flexible with regard to location and route of administration. Of enrolled subjects, 63% had either a typical or an atypical pathogen identified. However, nearly 25% had mixed infections, usually with a typical and an atypical pathogen. In an abstract presented at the Infectious Diseases Society of America annual meeting in San Diego, the subjects with CAP were pooled to determine whether there were different microbial pathogens on the basis of PSI class (table 1).

As shown in table 1, there was very little difference in the specific microbial etiology across the PSI severity classes. *Streptococcus pneumoniae* was the most common typical pathogen for all groups, followed by *Haemophilus influenzae*. Among the atypical pathogens, only *Mycoplasma pneumoniae* appeared more frequently in patients in PSI class I, relative to those in other PSI classes. The authors concluded that the etiology of bacterial pathogens was not different between PSI classes and, therefore, that the specific microbial cause of CAP was not the reason for differences in mortality observed by PSI scores.

Recently, our group at Replidyne conducted a detailed review of various Summary Basis of Approvals available on the FDA Web site or through Freedom of Information requests [9–13]. We selected CAP studies conducted since 1995 in which disease was not severe and in which a systematic search for both typical and atypical pathogens was conducted. As shown in figure 1, of 5025 evaluable subjects, 55% had no microbial etiology identified. Among the 45% who had an identified pathogen, approximately two-thirds had typical bacteria. *S. pneumoniae* was the most common typical pathogen, followed by *H. influenzae*.

We also conducted a review of published literature over the past decade of studies designed to determine the etiology of mild-to-moderate CAP. The results from >7400 well-characterized patients from 16 articles are summarized in figure 2. Again, *S. pneumoniae* was the most common typical pathogen, and *M. pneumoniae* was the most common atypical pathogen. Although the methodology of patient definitions may differ between these various sources of information, the similarity of the results strongly supports the frequency and importance of *S. pneumoniae* and other typical pathogens in mild-to-moderate CAP.

The critical point from these separate data sets is that *S. pneumoniae* must be accounted for in any CAP trial, even when the infection is not severe at the time the patient is enrolled. Mild or moderate CAP is not defined by the causative pathogen. It is appropriate to consider CAP as a continuum of disease of varying severity.

**HISTORICAL EVIDENCE OF THE BENEFIT OF ANTIMICROBIAL TREATMENT**

To conduct a scientifically rigorous noninferiority trial for CAP, we need to establish the benefit of antimicrobial treatment versus no treatment. Although this cannot be achieved through contemporary placebo-controlled clinical studies, it is clear to all that specific antimicrobial chemotherapy, first demonstrated with the sulfonamides, had a profound impact on patient mortality due to *S. pneumoniae* infection. In 1938, Evans and Gaisford reported a reduction in mortality from 27% to 8% in 2 cohorts of patients with “lobar” pneumonia [30]. Although the study was not randomized in a manner we would find acceptable today, it did have a contemporary and well-matched control group.

In 1939, following the sulfapyridine-dosing recommendations of Evans, Flippin et al. [31] reported a cohort of 100 patients with documented pneumococcal pneumonia who were admitted to several Philadelphia hospitals. In addition to the low (4%) mortality rate, they reported in detail the dramatic, rapid clinical response observed in their patients. Fully 83% had a substantial decrease in temperature within the first 48 h.

Although sulfapyridine chemotherapy and penicillin clearly had an impact on mortality, using mortality as an end point in a clinical trial for a new drug for treatment of mild-to-moderate CAP is not appropriate or feasible. Can we ascertain the benefit of antimicrobial therapy with regard to clinical response on the basis of published historical data? Although Flippin et al. [31] described clinical response among a cohort of patients given treatment with sulfapyridine, there was no control group. Another sulfapyridine experience was described by Agranat et al. [32] in 1939 for 550 patients from 3 hospitals in South Africa. Separate cohorts of patients either were given treatment with sulfapyridine or received only supportive care on the basis of their admission ward. In addition to describing the differences in mortality rates between treated and untreated cases, the authors described the timing of early clinical response, defined as “pyrexia termination.” Although there were many aspects of the patient cohorts that do not allow easy comparisons, the differences in clinical response matched the differences in mortality. A composite of the time to clinical response among patients who received treatment and patients who did not receive treatment is illustrated in figure 3. At day 3, the difference in clinical response was 55.6% (95% CI, 48.5%–62.7%).

One way of determining treatment benefit is to identify the natural or spontaneous course of disease when left untreated. In examining the preserum and preantibiotic data, we identified a detailed text written by Bullowa [33] in 1937 that documents the natural course of clinical resolution in 662 patients with pneumococcal pneumonia. This cohort of “survivors” received neither serum therapy nor chemotherapy. From this large data
set (figure 4), it is clear that spontaneous resolution does not occur rapidly. “Crisis,” the term used to describe the dramatic decrease in fever and initial clinical improvement, rarely occurs (rate, <3%) in the first 72 h and usually takes 7–9 days to develop, and, in 10% of Bullowa’s patients who survived, the initial resolution did not begin before 2 weeks of observation and supportive care. The observations of Bullowa [33] support those of Osler [34] in his 1910 version of Principles and Practice of Medicine and contrasts those in the 1942 edition written by Christian [35], when it was expected that a rapid clinical response would occur within 24–48 h after treatment with sulfapyridine.

What about “clinical response” in present-day circumstances? Again, we looked at the many CAP clinical trials conducted since 1995 and focused only on those subjects who were clinically or microbiologically evaluable. The data, shown in table 2, include >3600 clinically evaluable and 1175 microbiologically evaluable subjects. Among patients with mild-to-moderate CAP, the clinical response of cure or improvement was seen in nearly 92%, and there was a slightly higher rate among the microbiologically evaluable populations. It made no difference whether the pathogen was a typical or an atypical organism. What is striking from these data is the consistency among studies.

Although the clinical-response results from the clinical studies used to support New Drug Applications represent a dichotomous variable at a specific point in time after treatment, others have looked at time to response as a continuous variable. The cohort of 662 patients with S. pneumoniae pneumonia described by Bullowa [33] illustrates the timing of initial clinical improvement in spontaneously resolving cases. Petersdorf et al. [36] conducted a randomized, controlled trial of penicillin plus aspirin versus placebo, to determine the added benefit of antipyretic therapy for pneumococcal pneumonia. He designed a scoring system of clinical signs and symptoms monitored on a daily basis. Although he found no added benefit of acetylsalicylic acid treatment beyond 24 h, he did document the rapid (within 72 h) improvement in patient signs and symptoms among those given treatment with penicillin.

More recently, Halm et al. [37] and Mendenez et al. [38] characterized the time to clinical stability in hospitalized patients with CAP. Although the median response time of 3–4 days is relatively short, patients in both of these studies lacked microbiological diagnoses—in essence, clinical diagnosis was relied on for decisions about patient inclusion in the study. It is likely that the treatment response is more rapid for mild-to-moderate CAP when there is a specific microbial etiology treated with an appropriate antimicrobial.

Finally, at least 2 recent clinical studies of mild-to-moderate CAP have prospectively monitored time to response during a comparative noninferiority trial [39, 40]. In both studies, subjects received either a respiratory quinolone (gatifloxacin or moxifloxacin) or a standard treatment (a macrolide and/or amoxicillin). Despite the use of a “validated” patient-oriented questionnaire in the CAP 2000 study [41], both instruments were unable to distinguish between 2 very different active treatments (figure 5).

What can we conclude from these clinical trials and other historical clinical data sets? First, that clinical response in bacterial pneumonia treated with an appropriate antimicrobial drug is rapid, certainly when compared with spontaneous resolution in patients who survive pneumococcal pneumonia. Patients enrolled in clinical trials who have not improved clinically in 72–96 h are usually considered to reflect treatment failures and are reevaluated for alternative diagnoses, complications such as empyema, or the need for alternative antimicrobial treatment. Thus, there is historical evidence to support a large treatment benefit in early “clinical response” and not just in mortality. Second, there is no evidence to suggest that a time-to-response outcome instrument would be able to distinguish

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<table>
<thead>
<tr>
<th>Population</th>
<th>Clinical cure rate, % (no. of cases cured/no of cases treated)</th>
<th>Range of cure rates among studies, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>By subject</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically evaluable</td>
<td>91.8 (3379/3680)</td>
<td>86.3–96.5</td>
</tr>
<tr>
<td>Microbiologically evaluable</td>
<td>93.8 (1102/1175)</td>
<td>87.6–98.3</td>
</tr>
<tr>
<td>By organism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical bacteria</td>
<td>93.3 (513/549)</td>
<td>84.2–100</td>
</tr>
<tr>
<td>Atypical bacteria</td>
<td>93.4 (295/316)</td>
<td>73.9–100</td>
</tr>
</tbody>
</table>
Figure 5. Community-acquired pneumonia symptom questionnaire (CAP-SYMP) scores from the CAP 2000 study [39, 40] that compared moxifloxacin treatment with standard treatment. TOC, time of cure.

between 2 active treatments for CAP. This is not surprising, because we know that clinical response has more to do with host factors and disease severity than with specific drug-pathogen interactions.

SUPERIORITY TRIALS FOR MILD-TO-MODERATE CAP

The absence of contemporary placebo-controlled studies demonstrating the treatment benefit of antimicrobials for mild-to-moderate CAP might suggest the requirement for superiority trials to ensure the demonstration of efficacy. If placebo-controlled superiority trials are not ethical, what are the prospects of achieving “superiority” in an active-controlled study of mild-to-moderate CAP? The preponderance of data would suggest that this is unlikely to occur even when “stacking the deck,” as done by Petitpretz et al. [42] in a study that compared respiratory quinolone with amoxicillin and that was designed to enroll subjects infected with penicillin-nonsusceptible *S. pneumoniae*. Even with the added activity of moxifloxacin against atypical pathogens and with the selection of the subset of penicillin-nonsusceptible *S. pneumoniae*, amoxicillin was not inferior to moxifloxacin. There are at least 4 additional studies that compared a respiratory quinolone or macrolide with amoxicillin, all of which failed to demonstrate the clinical superiority that would be expected on the basis of in vitro susceptibility [43–46]. The recent change in penicillin-susceptibility breakpoints for *S. pneumoniae* is consistent with the results of these studies.

There is, however, a trial showing superiority of levofloxacin compared with a regimen of ceftriaxone followed by oral cefuroxime or with oral cefuroxime alone [47]. The patients in this trial were largely defined as having mild-to-moderate CAP. More than half were given treatment entirely as outpatients, and this meant that half of the cephalosporin group received only oral cefuroxime. On the basis of the FDA Medical Reviewer’s assessment, levofloxacin was superior to the cephalosporin regimen for both the clinically evaluable and microbiologically evaluable populations (table 3) [9]. It is important to note that cefuroxime is not approved for treatment of CAP in the United States, and the dose used, 500 mg twice a day, is one-third the dose recommended in Europe for initial treatment of CAP. Nevertheless, although cefuroxime as used in this trial may be considered “subtherapeutic,” the study regimen of ceftriaxone and/or cefuroxime is still likely better than placebo. This study is important because it demonstrates the clinical and microbiological superiority of levofloxacin in a contemporary clinical trial, one that was carefully reviewed by the FDA and that provided a superiority claim in the package label [48]. The observed difference in clinical response rates of 12% for the clinically evaluable population and 16% for the microbiologically evaluable population underestimates the real M1 benefit of levofloxacin versus no treatment, given the likelihood that the cephalosporin regimen had some treatment effect. Although this study has not been reproduced, we believe it provides one approach to justifying a noninferiority margin for mild-to-moderate CAP.

DETERMINATION OF A NONINFERIORITY MARGIN FOR MILD-TO-MODERATE CAP

Because, according to ICH guidance E10 [4], use of a previous superiority trial is an alternative to use of a placebo-controlled trial, the demonstration of superiority of levofloxacin in clinical response, compared with a cephalosporin regimen, provides one approach to defining a noninferiority margin for future trials for mild-to-moderate CAP. Once the benefit over an active control, or M1, is established, the next step is to determine the noninferiority margin, M2. No process is provided in either the FDA’s new guidance or ICH guidance E10. We know M2
“cannot be greater than the smallest effect that the active drug would be reliably expected to have” [4, p. 10]. If the cefalo- sporin regimen of ceftriaxone and/or cefuroxime has a clear but not quantified benefit over placebo, then the superiority of levofloxacin of 12% for the clinically evaluable population and 16% for the microbiologically evaluable population would support a noninferiority margin of 10% for the clinically evaluable population and 15% for the microbiologically evaluable population.

Another approach to justifying the noninferiority margin is derived from the historical data. First, by examining the clinical-response curve (figure 3) from the study by Agranat et al. [32], the largest difference between patients who received treatment and patients who did not receive treatment is 55.6% on day 3. The lower boundary of the 95% CI is 48.5%. Using 48.5% as an estimate of M1, one can conservatively preserve 50% of the treatment benefit with a noninferiority margin of 24% for a clinically evaluable population. This calculation is supported by the historical data from Bullowa [33] on clinical response among patients who spontaneously recover while receiving no therapy for documented pneumococcal pneumonia. The data from Bullowa represent the best “placebo” group, in which clinical response, and not mortality, was the outcome measured. If we accept the evidence-based premise that spontaneous clinical response rarely occurs in <72 h, whereas lack of clinical response in that same time frame would be considered a treatment failure in the antibiotic era, then the benefit of antimicrobial treatment is quite large. To define M1, we can use the observed clinical response of 93.8% of microbiologically evaluable subjects, derived from recently approved drugs for treatment of mild-to-moderate CAP [9–13]. To account for variability and to be conservative, we take the lower boundary of the 95% CI around this observed rate, which is 91.3%. We then multiply this times the percentage of clinically evaluable subjects expected to have typical bacterial pathogens, estimated as 35%. This determines the M1 of 31.9%. Then, to determine the noninferiority margin for future studies, M2, we conservatively take 50% of the M1, or 15.9% for the clinically evaluable population. Given the fact that the data from Bullowa included only documented bacterial pneumonia in patients who did not receive treatment, we cannot estimate a noninferiority margin for the clinically evaluable population. Notwithstanding the fact that CAP is caused not only by pneumococcus and that supportive medical care has improved since the preantibiotic era, the treatment effect in documented bacterial CAP is large, in terms of both clinical response and mortality.

### WHAT POPULATION IS IMPORTANT IN STUDY DESIGN ANALYSIS?

We have presented data for both clinically evaluable and microbiologically evaluable subjects. The distinction is important because which population is primary in the study analysis will determine the study sample size. The FDA prefers 2, or “co-primary,” populations in the analysis of noninferiority studies. In the past, these have been the clinically evaluable and intent-to-treat (ITT) populations. Currently, the FDA is requesting use of the clinically evaluable population and the modified ITT (mITT) population, defined as ITT subjects with a microbiological etiology, as the coprimary populations. Because the mITT population represents a much smaller subset of patients, estimated here as 30%–35% for typical pathogens, than the clinically evaluable population, a study that was previously sized to show noninferiority with a 10% margin with 484 enrolled subjects would now require nearly 1200 subjects if the same 10% margin is applied to the mITT population. However, if the noninferiority margin applied to the mITT population was 15%, the sample size would be 556, a number much closer to the study size for the 10% margin for clinically evaluable subjects.

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**Table 3. Comparison of levofloxacin versus ceftriaxone and/or cefuroxime for treatment of mild-to-moderate community-acquired pneumonia in a multicenter, prospective, randomized, open-label study.**

<table>
<thead>
<tr>
<th>Population</th>
<th>Clinical response rate for levofloxacin</th>
<th>Clinical response rate for ceftriaxone and/or cefuroxime</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically evaluable</td>
<td>95</td>
<td>83</td>
<td>−12 (−18.6 to −6.2)</td>
</tr>
<tr>
<td>Microbiologically evaluable</td>
<td>96</td>
<td>80</td>
<td>−16 (−23.5 to −7.4)</td>
</tr>
</tbody>
</table>

**NOTE.** Diagnoses were made by sputum and blood culture, direct fluorescent antibody and urinary antigen testing for Legionella pneumophila, or serological analysis for atypical pathogens. Data are from [9].

- The total population was 590 patients (295 per arm): 53% were outpatients, and 84% had mild-to-moderate infection. Patients were ambulatory or hospitalized.
- Levofloxacin given at 500 mg once a day (intravenously or orally) for 7–14 days. Of those who received levofloxacin, 61% received oral treatment.
- Ceftriaxone (1 or 2 g) once a day and/or cefuroxime (500 mg) twice a day for 7–14 days. Of those who received ceftriaxone and/or cefuroxime, 50.4% received oral treatment.

(continued...)

**Populationa**

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A PROPOSAL FOR MILD-TO-MODERATE CAP

This brings us to a proposal for a noninferiority study design for mild-to-moderate CAP in which the coprimary populations are the clinically evaluable and mITT populations. On the basis of the trial of levofloxacin versus ceftriaxone and/or cefuroxime, a noninferiority margin of 10% for the clinically evaluable population is justified. From the historical data from Agranat et al. [32], we can estimate a large treatment benefit for early clinical response, which would support a noninferiority margin >10% for clinically evaluable subjects; however, in an effort to avoid biocreep, the 10% noninferiority margin would suffice. Furthermore, on the basis of both data from the levofloxacin study and the historical data from Bullowa [33] on clinical response in documented bacterial pneumonia, a noninferiority margin of 15% for the microbiologically evaluable or mITT population is justified. Note that the noninferiority margins for the coprimary populations are different. With a coprimary analysis designed to have 90% power overall, the sample size for 1 study would now be 618 patients, an increase from 556. Under the assumption that 2 trials are required for approval, the total number of patients with CAP would need to be 1236. Although we do not suggest the pooling of the 2 studies to add an additional hypothesis, it is important to note that there is adequate power, >85%, to show noninferiority using a 10% margin for the pooled mITT or microbiologically evaluable populations.

SUMMARY

The evidence supports the fact that CAP represents a continuum of disease caused by similar pathogens and not distinct entities dependent on a severity score or the ability to comply with oral antimicrobial treatment. In many patients, mild-to-moderate infection, if left untreated, is likely to progress to more-severe infection. Furthermore, patients with mild CAP may not experience the same mortality as that experienced by patients in PSI classes IV and V, but the data indicate that, if these patients do not receive treatment, they will experience slower clinical resolution than will patients who receive treatment.

Second, although the statistical reasoning that favors superiority studies is recognized, neither placebo-controlled nor active-controlled superiority trials for CAP are feasible, even for mild-to-moderate CAP. Placebo-controlled studies for CAP would be considered unethical by most institutional review boards or ethics committees. The use of alternative outcome measures, such as time to response or a patient response–oriented questionnaire, in an active-controlled superiority trial has not been shown to be sensitive to a treatment benefit between 2 acceptable antimicrobial regimens.

Third, noninferiority margins for mild-to-moderate CAP can be justified using clinical judgment and statistical reasoning. On the basis of both historical data from the preantibiotic era and data from contemporary active-controlled clinical trials, the treatment benefit of antibiotics can be estimated for clinical response. Our suggested methods are consistent with ICH guidelines.

Fourth, the question is not only what is the absolute noninferiority margin but also what populations will be included in the primary analyses. The impact of this decision will greatly influence the sample size and, thus, the feasibility of the trials. The mITT population analysis is inherently attractive because it focuses on subjects with microbiologically identified infections; however, an mITT analysis represents only a subset of the subjects enrolled using clinical and radiographic criteria. Given the relatively insensitive current diagnostic methods for CAP, the absence of a microbiologically confirmed etiology does not exclude a bacterial cause. CAP caused by typical bacterial pathogens is more likely to respond rapidly to appropriate antimicrobial treatment; thus, a larger noninferiority margin can still preserve evidence of efficacy. Each population needs to have a noninferiority margin based on available data and reasoning, even though the margin may be different.

Finally, the determination of the specific details of clinical trials to support regulatory approval for new antimicrobial drugs for treatment of CAP is essential and not just an academic exercise. There is a need for regulatory clarity and a definitive transparent decision on the major questions of study design. Without regulatory clarity and an acceptable path forward, new investments in antimicrobial drugs will continue to diminish.

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