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Regulatory Pathways for New Antimicrobial Agents: Trade-offs to Keep the Perfect From Being the Enemy of the Good

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Abstract

In 2002, Shlaes and Moellering warned that pharmaceutical companies were abandoning antibiotic research and development due to changing regulatory standards regarding noninferiority (NI) clinical trials. NI trials are subject to unique biases that may yield false-positive conclusions. The US Food and Drug Administration (FDA) developed guidance to ensure that NI results truly reflect drug efficacy. These changes, intended to reduce uncertainty in trial results, have shaped trial enrollment and conduct in ways that now require reflection.

CHANGES TO ANTIMICROBIAL CLINICAL TRIALS

Although prior antimicrobial noninferiority (NI) trials often used 15–20% NI margins, new guidances increasingly suggest 10% NI margins (Supplementary Table S1 online), while indicating that the margin for a specific drug and trial needs to be individually justified.[1,2] Moving from a 15% margin to a 10% margin requires an approximate doubling of the sample size to achieve the same statistical power, increasing the study cost and duration.

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CONFLICT OF INTEREST

In the last 12 months, B.S. has received consulting fees from Cempra, The Medicines Company, MedImmune/AstraZeneca, PTC Therapeutics, Entasis, Tetraphase, Merck, and Genentech, DSMB fees from Dipexium, and owned equity in Motif, BioAIM, and Synthetic Biologics. In the last 12 months, K.M. has received consulting fees from Amplyx, Avaxis, Chimerix, Cidara, F2G, Incyte, Genentech, Merck, Revolution Medicines, Theravance, and Vical, and owned equity in MycoMed Technologies. E.P.B. has received consulting fees from GSK, Sigma-tau Pharmaceuticals, McNeil Consumer Pharmaceuticals, Concentrics Research, Novo Nordisk, 3D Communications, Catabasis Pharmaceuticals, Bayer, Takeda, Galderma, ContraFect, Hyrda Biosciences, Ataxion, Akros Pharma, Consumer Healthcare Products Association, and Novartis, and owned equity in Calistoga Pharmaceuticals (now owned by Gilead) and Catabasis Pharmaceuticals.

Additional Supporting Information may be found in the online version of this article.

Another common change has been to restrict subject eligibility based on receipt of antimicrobial therapy before randomization. Prestudy treatment may increase success rates and, thus, bias the difference in treatment arms toward the null. However, the standard of care in the US and Western Europe is rapid initiation of broad-spectrum antibiotics for seriously ill patients. The practical result of a prohibition on antecedent therapy is to eliminate enrollment of seriously ill patients and/or to shift enrollment to countries with a different standard of care. In either case, the apparently more rigorous data will be at the expense of generalizability, and likely overall disease severity enrolled.

Conversely, for agents lacking an oral formulation (reflective of the large majority of antibiotics in development), concerns about the confounding effect of stepdown therapy to an alternate oral agent have resulted in the need to administer prolonged i.v. therapy in inpatient settings. The tradeoff effect of requiring prolonged i.v. therapy in the hospital is to make it more difficult to enroll patients who are not severely ill and do not require prolonged hospitalization. In the US, there is tremendous pressure from payers and safety/quality improvement efforts to shift patients to the outpatient setting as soon as possible. Thus, it is difficult to find patients who are both stable enough to wait multiple hours to initiate antibiotic therapy so enrollment can occur before antibiotics are administered, while being sick enough to require multiple days of inpatient hospitalization.

These study design changes intended to reduce uncertainty in decision-making simultaneously reduced the eligible study population while mandating larger sample sizes. As a result, recent pivotal trials of antimicrobials have enrolled patients primarily (>90–95%) outside the US, often in countries having substantial differences in standards of care compared to the US and Western Europe.[3–6] Even when performed to the highest ethical and scientific standards and using Good Clinical Practice across geographic distributions, this change in geographic enrollment driven by differences in clinical practices creates challenges for both regulators and practicing physicians as to how the results should be used to inform regulatory decisions and clinical practice.

Thus, at the same time, the US Food and Drug Administration (FDA) mandated enrollment of more patients with more restrictive enrollment criteria out of a desire to enable more precise estimates of treatment effects, trial risks becoming less generalizable and informative to providers and patients in Western countries.

RECENT EXAMPLES OF REGULATORY ACTIVITY AND CLINICAL IMPACT

Ceftolozane-tazobactam began its development program with two parallel enrolling trials for complicated urinary tract infection and two for complicated intra-abdominal infection (cIAI).[3,4] The trials used enrollment criteria consistent with the FDA guidances and experienced slow accrual over 2 years. Subsequently, the company compressed each pair of studies into single trials for each indication, facilitating their completion.[3,4] The drug was shown to be noninferior to levofloxacin for treatment of complicated urinary tract infection.[3] However, results of the cIAI study raised important questions, as the point estimate (95% confidence interval) for the treatment difference was −4.2% (−8.9% to 10.5%).[4] The study was positive, having met the NI criterion with the lower bound above −10%. However, if the

range of the 95% confidence interval were assumed to represent a valid estimate of the probability distribution of the true effect size, analogous to a Bayesian probability interval, then that would suggest that the new drug is likely to be truly inferior to the comparator because the majority of the confidence interval was negative. Furthermore, only 5% of patients were enrolled in North America, and Eastern Europe contributed 78% of all patients to the trial; these latter subjects had cure rates of 96%, substantially higher than anticipated during the trial design, and likely reflective of enrollment of patients who would not be sick enough to be hospitalized in the US. This high cure rate would bias the NI trial toward the null (difference of 0.00%), making the observed −4.2% even more surprising. There was also increased mortality in the experimental arm across the phase II and III trials for cIAI.[7] Although the drug was approved in 2015 by the FDA with an indication for both complicated urinary tract infection and cIAI, the trial results create concern about using ceftolozane-tazobactam to treat cIAI if alternative drugs are available. Unfortunately, as clinicians often view an NI result as inappropriately meaning “as good as,” the FDA’s acceptance of the cIAI indication may increase use of a potentially inferior drug and risk worsened outcomes for some patients.

Had the trials been more facile to enroll, two separate trials for each indication may have been completed, which would have both: (1) enabled greater precision around the cIAI success rate, including a population more reflective of US inpatients; and (2) enabled approval of the drug based on two trials for complicated urinary tract infection without the cIAI indication, if the latter dataset did not provide compelling evidence of efficacy.

As another recent example, isavuconazole was approved in 2015 for the treatment of both aspergillosis and mucormycosis. Although aspergillosis was supported by a large randomized trial, clinical data supporting approval for mucormycosis was based on a small (n = 37), underpowered, open-labeled, uncontrolled cohort study, with “matched” patients drawn from an unrelated cohort.[8] Despite the small sample size, lack of a prospective control group, lack of randomization, and nonblinded study drug administration, the FDA granted an indication for the treatment of mucormycosis. As isavuconazole was approved for the treatment of invasive aspergillosis, failure to grant an indication for mucormycoses would not have limited its availability for selected patients with mucormycosis requiring alternative therapy. Experts continue to believe that isavuconazole should not be used as a first-line treatment option for mucormycosis.[9] However, again, clinicians may interpret the FDA indication as an indication of equivalency of efficacy of isavuconazole to standard first-line therapeutic options for mucormycosis, despite the very limited dataset that served as the basis for approval. Ironically, the granting of isavuconazole’s approval for mucormycosis based on the 37 patient open-label trial without an active control may have made a proper trial less likely to be conducted in the future, because sponsors will see no reason to do so.

WHAT IS THE PATH FORWARD?

Tradeoffs between reducing uncertainty in anti-infective drug approvals and the ability to generate high quality data have shifted to the point that paradoxically less robust data are being used and less clinically relevant information is being provided to clinicians about

approved drugs. To restore this balance, several practical steps should be considered, recognizing that the considerations need to be drug, indication, and trial-specific.

A LIMITED AMOUNT OF PRESTUDY ANTI-INFECTIVE THERAPY SHOULD BE ALLOWED

Allowing 24 hours of prestudy therapy enables enrollment in the context of how medicine is practiced in Western countries, with the specific permissible therapies dependent on the organisms and sites of infection being studied. Equally important, it allows enrollment of sicker patients for whom immediate initiation of anti-infective therapy is the standard of care. The risk of bias toward the null from pre-study anti-infectives must be balanced against the need to enable enrollment of more severely ill patients so that trial results are generalizable and inform clinical practice in the US and Western Europe.

OPTIMIZE TRIAL RELEVANCE TO PATIENTS IN THE US AND WESTERN EUROPE

Although international trials are to be encouraged, enrollment criteria must make it facile to enroll populations of patients relevant to how the drug will be prescribed postapproval. Some acceptance of bias toward the null may be necessary as a tradeoff to such enrollment feasible. Attention should be paid to ensure consistency in background therapy and trial results should be reported by relevant geographic subgroups to allow any differences to be identified. If geographic discordance is observed, efforts should be made to identify contributing clinical explanatory factors. Meaningful representation of patients from the US and Western Europe in trials will facilitate this assessment.

EARLY TRANSITIONS TO ORAL THERAPIES AND/OR HOME INFUSIONS SHOULD BE ALLOWED IN TRIALS

In contemporary clinical practice, short course intensive anti-infective treatment is followed by home treatment, often with a different anti-infective. For drugs with no oral formulation, allowing home i.v. therapy can allow the patient to leave the hospital, which is necessary for enrollment in the US. Furthermore, allowing home i.v. therapy and/or early switch to oral regimens with a nonstudy drug in clinical trials will both enhance recruitment and better reflect postapproval clinical use. Concerns about poststudy drug treatment determining clinical outcome can be minimized by defining objective criteria for the transition of care.

USE OF NOVEL TRIAL DESIGNS TO MAXIMIZE INFORMATION AND MAKE TRIALS MORE EFFICIENT

There are opportunities to improve our understanding of new (and old) drugs by using more innovative development approaches. Bayesian adaptive designs, currently used in early development, could be used to allow earlier initiation of phase III trials and to more efficiently refine understanding of dose requirements, antimicrobiologic profile, and impact of infection site on efficacy.[10] Inclusion of patients with infections across multiple body

sites, focusing on particularly antibiotic-resistant pathogens, will enable more rapid enrollment while focusing development on true unmet needs. The experience with ceftolozane-tazobactam indicates the importance of controlling for variations in effect size by body site in such trials; methodologies to achieve this are available.[10]

Importantly, implementing innovative approaches may result in greater uncertainty about a drug's true efficacy. This should be acknowledged in a transparent manner while endeavoring to minimize biases, which may contribute to this uncertainty. However, any innovative design must meet the regulatory standard of providing substantial evidence of efficacy based on adequate and well-controlled data if used as the basis for a label indication. Clinicians need to be aware of the strengths and weaknesses of innovative strategies to optimize their own prescribing behaviors.

If recent examples of antimicrobial approval perpetuate, our efforts to improve precision of anti-infective clinical trials may ultimately serve to introduce more uncertainty in drug efficacy, as clinical trials become infeasible to conduct and not generalizable. Clinicians must be able to understand and act on trial results. It may be time to take another road to address the challenges inherent to anti-infective trials and fundamentally rethink the design and review considerations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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