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Tribulations of trials for antibacterial drugs: interview with Sumathi Nambiar

Sumathi Nambiar is deputy director for safety in the division of antiinfective products at the US FDA. He has participated in discussions between industry, academia and regulatory bodies in workshops designed to address the current concerns regarding non-inferiority design in antibacterial trials, and has also contributed towards the follow-up guidance released by the FDA. Sumathi Nambiar spoke with Laura Harvey at *Clinical Investigation* on some of the key issues facing clinical trials in this arena.

Recent guidance

• What would you say were the most pertinent points raised in light of the recent FDA re-evaluation of non-inferiority trials as a means of assessing drug efficacy for bacterial diseases and the following workshops, and what effect do you see these having on the end points chosen for these trials?

The most pertinent points raised are that the design of non-inferiority trials should be based on sound scientific principles, be evidence-based, ethical and feasible. It is important that these trials enroll patients with the clinical condition being studied, including in many instances microbiological evidence of a causative pathogen. It is also important that appropriate end points are utilized, both in terms of definition of the end point and timing of assessment. The non-inferiority margin should be prespecified, based on historical evidence of treatment effect for the active comparator and be reliable and reproducible.

Q What effect do you see the new regulatory guidance having on drug development, particularly for the treatment of antibiotic resistant-bacterial infections?

While we recognize some of the practical difficulties in the conduct of clinical trials for antibacterials, it is also important that these trials be done with scientific rigor such that meaningful inferences can be drawn. The availability of new drugs and of treatment options is a key priority for us. However, it is also important that the clinical trials done to evaluate such therapies be scientifically sound and provide meaningful treatment benefit to patients. These trials should provide information to better characterize the effects of an antibacterial drug which in turn can help foster appropriate and judicious use of antibacterials.

Q The non-inferiority design of antibacterial trials means new therapy has to be shown to be as effective as comparator therapy. However, most therapies in the market precede wide-spread, randomized placebo-controlled studies – what knock-on effect would you say this has had on the assessment of



effectiveness of current treatments being tested with the non-inferiority design? Do you think this requires a restructuring?

Non-inferiority trials show that the test drug is no worse than the comparator by a predefined and clinically acceptable margin based on historical evidence of treatment effect. Two principles that underpin the reliability of a non-inferiority margin determination are assay sensitivity and constancy of control treatment effect. As non-inferiority trials for antibacterials lack a no-treatment or placebo-control arm, data external to the trial that reliably estimates the magnitude of treatment benefit of the active control is essential. Therefore, a critical factor for a non-inferiority trial is whether the active control drug would have been able to distinguish itself from a placebo or no treatment in the condition under study. In circumstances where one cannot reliably distinguish the effect of the active control from a placebo or no treatment by a set amount, a valid non-inferiority trial cannot be conducted.

Primary end points

Q How does the typical structure of antibacterial trials (non-inferiority) affect the end points chosen and therefore the meaning of results? In terms of these end points, what do you think they should reflect?

The end points chosen for non-inferiority trials should be reliable and clinically meaningful as with all other types of trials. An additional factor in non-inferiority trials is that a scientifically valid justification of the noninferiority margin must be possible for that end point (definition of the end point and timing of assessment).

• Certain primary efficacy end points can fail in a number of ways. How does this affect trial interpretation? If X number of patients fail to reach the primary end point, surely if there are a number of ways that a patient can fail to meet this criteria then this statistic is somewhat opaque?

While there may be more than one way to fail, each of the components of a failure end point will need to be analyzed separately as well. Although, the overall failure rate is important, it is essential to understand the reasons for failure in assessing the results of the trials.

Q How would you assess the statement that primary end points should reflect how a patient feels, functions or survives in order for trial results to be meaningful to patients in any real way? While it is important that the end point captures how a patient feels, functions or survives, there is still value to a clinician's assessment of clinical response or lack thereof. Although there are concerns that the clinician assessment can introduce some element of subjectivity, decisions made by the clinician regarding the overall clinical response is based in great part on how patients feel and function and also takes into consideration other important characteristics such as objective clinical signs.

"It is also important that the advice given at this time is durable and remains valid by the time the trials are completed."

• One of the main criticisms of antibacterial trials is that end point assessment, often based on investigator assessment without objective criteria, is very subjective. What would you say in response to this statement and what difficulties arise in trying to address this issue?

For clinician-reported outcomes, it is important to standardize the outcome measures so that variability amongst the investigators can be minimized. While evaluating symptoms may establish how a patient feels or functions it is important that the measurement tools used are validated. Often, finding historical evidence to support a non-inferiority margin justification on the basis of patient-reported outcomes - how a patient feels or functions - can be difficult. Information on how FDA qualifies new efficacy end points can be found in the draft guidance, 'Qualification Process for Drug Development Tools' [101]. While the work on qualification of a new end point is underway, it is important that clinical assessment be evaluated in conjunction with symptom resolution/improvement. While patientreported symptoms alone may be appropriate for some clinical conditions, they may not be appropriate or optimal for other clinical conditions.

• Would you say that this subjectivity is more the case when the assessment is made later on in the trial?

Any outcome assessment that is performed very late in the course of a clinical illness that has a considerable degree of spontaneous resolution can be misleading, irrespective of whether the assessment is based on symptoms or investigator assessment of clinical response. Assessments at a later time point are challenging when the treatment effect is seen early in the clinical illness and no clear treatment effect is seen later in the course of the illness or the evidence supporting a treatment effect at the later time point is lacking. Hence, rather than the issue of subjectivity, the concern is regarding the demonstration of a treatment effect at a later time point.

Mortality as an end point

Q Although mortality is historically well established as an end point, how would you assess the advantages and disadvantages of this end point given that it is only high for very small/specific subgroups?

Mortality can be assessed as part of an end point or can be an end point by itself. Often, mortality will be included as part of a composite or a responder end point. Mortality as an end point has the benefit of being objective, however, in certain clinical conditions it may not be an appropriate end point. Often, the mortality rate in the disease being studied is low making trials based on a mortality end point infeasible due the large sample size that would be required.

Q What are your opinions on the FDA estimate of the mortality effect size? Do you think this is accurate?

As an appendix to the recently published draft guidances, we have provided justification for the noninferiority margin and our assessment of the treatment effect size. While these data have limitations, especially with respect to changes in standard of care and in the patient population studied, we are limited by the quantity and quality of historical data available. We have put forth our best effort to describe our approaches to defining non-inferiority margins.

• Composite end points have been suggested as an alternative to mortality as a primary end point. What would you say are the advantages and disadvantages of composite end points and how would you recommend that the results of composite end point analysis be treated such that statistical trends are not obscured?

A composite end point is justified if the individual components of the composite end points are clinically meaningful, and the expected effect on each component is of similar importance to patients. Composite end points can be problematic when the response is driven by any one of the different components of the end point. On the other hand, in a responder end point, success is declared only if one wins on all the components of the end point and not any one of the components as in a composite end point. For a composite end point, it is important to analyze the individual components to evaluate the consistency and direction of the treatment effect.

Timing of end point assessment

Q Timing of end point assessment is also an issue, as it is now possible to microbiologically assess disease development, progression and regression during a trial. Improvement can be seen as early as 3–5 days with some diseases, raising the questions as to the timing of end point assessment. What is your opinion on the timing of end-point assessment and the factors that need to be taken into account in deciding when to assess?

In any clinical trial, timing of the end point assessment should be clinically meaningful and in non-inferiority trials it is also important that the timing of assessment be supported by evidence of treatment effect for the active comparator. Another important factor in choosing the timing of the end point is the natural history of the disease, as in some clinical conditions, spontaneous resolution can occur over a period of time and hence the effect of the intervention is only noted at an earlier time point.

• For cases where symptoms do not resolve but improve, the definition of 'improvement' needs to be standardized in order to assess certain, nonbinary end points. What implications does this have for trial design, ease of assessment and inclusion criteria?

If the end point is based on improvement rather than resolution, it is crucial that the definitions be standardized, ideally using a validated instrument. In terms of implications on trial design and inclusion criteria, it is important that the variables being assessed are relevant to the type of patients being enrolled and that meaningful assessments are not being confounded either by underlying illnesses or possibly concomitant medications.

Concluding remarks

Q What effect do you see the regulatory uncertainty in antibacterial trial design having on further research into developing much-needed effective treatments?

The ongoing effort to develop recommendations on scientifically sound, ethical and feasible clinical trial designs is important and can help address scientific issues leading to uncertainty in the field of antibacterial drug development. Important work in characterizing clinical end points is being done by the Foundation for the NIH. The Foundation for the NIH project team includes representatives from academia, the pharmaceutical industry and government organizations such as the FDA and NIH. As the field moves forward, some uncertainty will be addressed as clinical trials are completed for a particular indication. It is also important that the advice given at this time is durable and remains valid by the time the trials are completed. We do acknowledge the difficulties and challenges in doing these trials and at the same time realize the importance of designing and conducting these trials in a scientifically rigorous manner.

Financial & competing interests disclosure

Sumathi Nambiar has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

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