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Tribulations of trials for antibacterial drugs: interview with Joseph Kuti

Following draft guidance from the US FDA in March 2009 [1] on trials to assess antibacterial agents for community-acquired bacterial pneumonia, there has been much debate between industry, academia and regulatory bodies on the issues faced in the design of such trials. Follow up workshops and guidance [2,3] have contributed to the active discussion on the topic, highlighting the increasing urgency of bringing effective therapies to market in the wake of increasing strains of multidrug resistant bacteria. Joseph Kuti, Brad Spellberg, Sumati Nambiar and Mark Leuchtenberger and Scott Hopkins all spoke with Laura Harvey at *Clinical Investigation* on some of the key issues facing clinical trials in this arena. Joseph Kuti sits on the *Clinical Investigation* editorial board and is the associate director of Clinical and Economic Studies at the Center for Anti-Infective Research and Development at Hartford Hospital, Connecticut and also holds an Adjunct Assistant Professor appointment at the University of Connecticut School of Pharmacy. Kuti's research interests include the pharmaco-kinetics, -dynamics, -economics and outcomes of antimicrobial therapy in severe infections.

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Recent debate

Q What would you say were the most pertinent points raised in light of the recent US FDA re-evaluation of non-inferiority trials as a means of assessing drug efficacy for bacterial diseases and the following workshops?

I think the most important point highlighted at these discussions is that antibiotic development has unfortunately stagnated in the face of increasing resistance. The objective of all parties involved should therefore be to make the regulatory process as simple as possible while maintaining scientific integrity. I think the re-appearing discussions surrounding the need for placebo-controlled trials is unrealistic, even for mild infections, and certainly shouldn't apply for life-threatening infections such as pneumonia and complicated skin infections – all parties appear to agree on the latter. There has also been a lot of discussion surrounding the use of mortality as an end point, and what a 'superiority' design might look like, the latter of which might be needed for the development of new antibiotics against multidrug-resistant bacteria, where currently few available antibiotics could even be considered as a comparator and even fewer have a FDA indication for the infection in question. Clearly new rules and regulations will have to be developed to guide industry into this yet untouched but critical area of development.

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

No one can make pharmaceutical companies develop these drugs – they are going to have to want to do it, and without appropriate guidance, it has not been an easy process for the companies that have submitted new drug applications in recent years.

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But I suspect if the guidance is set and the rules are in place, pharmaceutical companies will be enthusiastic about developing new antibiotics.

Q The non-inferiority design of antibacterial trials means new therapy has to be shown 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?

I have already alluded to my thought that placebo-controlled trials would be unrealistic to perform today for most infections. Can you imagine a parent wanting to enroll their child in an acute bacterial otitis media trial where there is a chance they could receive placebo? Until a consensus is made on the clinical side that antibiotics are no longer needed for these types of mild infections (and we are still a way off from that), we are going to need new antibiotics for these indications. Therefore, the value of placebo-controlled trials would only be to determine what the actual antibiotic effect is on a specific end point, and thus what the lower bounds of the margin should be for proper assessment of non-inferiority. To address this, investigators have to go back to the days when antibiotics were not available, when data were unfortunately often difficult to interpret, but that appears to be the best we have got right now. The danger in these ongoing discussions, however, is that the goal posts may be moved after the ball has already been kicked – and we have certainly already seen this occur for a number of recent responses from the FDA, both for drugs that have not yet received approval as well as for those that have. So, I am not sure it needs re-structuring as much as we need to come to a consensus and stick with it, until better evidence tells us to do something different moving forward.

Q Can you clarify what you mean by better evidence?

The guidance for conducting clinical trials and the appropriate measures seem to be continuously changing. For example the FDA's *post hoc* analyses of ceftaroline for community-acquired bacterial pneumonia (CABP) and complicated acute bacterial skin and skin structure infections (ABSSSI) used day 3 and day 4 end points, and this is what went into the label and were used for the final decision-making process. That evidence, which was used to make their decisions, is outlined very nicely in the review of ceftaroline on the FDA website [1]. [In the review] they go through all the limitations of their *post hoc* analysis and although that [method] may be the best we have right now, someone in the future might discover a better way to do it. If and when that happens, as our knowledge progresses, the question still remains when is the best time to institute that new evidence? Should it be instituted right then moving forward even if a trial hasn't been finished? Should it be applied to studies that have been completed already, even if that trial was not designed with those end points in mind? Or should it only be used for studies that are getting started? I think the FDA wants to review the data based on the best evidence for end points and then apply this to current studies. However, I can sympathize with the developers' point of view, in that the study wasn't originally designed to address such end points in the first place. In the recent ceftaroline example, the *post hoc* review agreed with the trial end point results quite nicely but I don't always see that happening.

Primary end points

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

There are several problems with the current non-inferiority design. To touch upon a few: the comparator has to be carefully selected as a drug that is already FDA approved for that indication, which may not always coincide with the typical way an infection is treated clinically. Additionally, if an organism is known to be resistant to the comparator, patients infected with it have to be excluded from the trial, even if the tested antibiotic might have potential activity. However, then could a new antibiotic ever be shown in its true light? A great example of both of these concerns applies to the recently approved ceftaroline, as seen in CABP studies. First, the standard of practice, particularly in the USA, is to provide combination therapy (e.g., a macrolide) to cover for intracellular organisms that ceftaroline and its comparator, ceftriaxone, would not have activity against. This standard of practice discrepancy led to two different trial designs, one permitting only a single day of clarithromycin and a second with no such combination permitted. One could, and should, ask what the effect of a single day's worth of clarithromycin had on pathogens and interpretation of differences? Should the two studies be interpreted differently? This certainly led to few patients enrolled in the USA, where the drug is now approved and clinical guidance clearly suggests the use of a second antibiotic concomitantly. Second, although ceftaroline has *in vitro* activity against methicillin-resistant *Staphylococcus aureus*

(MRSA), patients with these organisms were excluded because of ceftriaxone's lack of activity. CABP caused by MRSA is a rare but growing concern in the USA, and unfortunately we have no clinical data for ceftaroline in this area. There are other often-noted concerns with non-inferiority designs (including the need to defend the non-inferiority margin), but at the end of the day, all of these issues potentially make for a decision surrounding a drug that does not reflect current clinical practices or needs.

Q How would you assess the statement that they (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?

I don't think these apply to infection as primary end points. However, this is where outcomes research can be better incorporated into trials. Most infections are acute events, so applying long-term quality-of-life indicators would not always be relevant, plus these tools are not yet available or validated. That being said, since at the end of the day, most new antibiotics will only ever be found to be non-inferior to their selected comparator, having outcomes research data will be important, particularly surrounding speed of recovery and potential tolerability/toxicities. These secondary end points could be most useful in helping clinicians decide how to best choose and position these new drugs in daily clinical practice. I would like to see more of this.

Q 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 difficulties are there in constructing an end point such that it is more objective and implementing specific defining criteria? Do you have any suggestions for an approach to choosing specific criteria of particular relevance for a given trial?

Well herein lies the challenge. How to objectively determine a new therapy will be as effective, if not better, than a currently available one, while doing this in a way that emulates how a prescriber makes a decision to continue, discontinue or change therapy in the clinic. We have now witnessed the new recent guidance indicating mortality as a primary end point for hospital-acquired pneumonia trials, but that end point is still all cause mortality at 28 days. It will be interesting to see how drug developers design new studies incorporating this end point, and how it correlates with the more subjective test of cure assessments for the trial populations. We have also seen *post hoc* objective assessments at day 3 and 4, respectively for ABSSSI and CABP, with ceftaroline. Fortunately, this provided further evidence into ceftaroline non-inferiority, but there were also clear limitations noted by the FDA reviewers in the application of these objective end points. Importantly, now that they have been established, I see no reason why future ABSSSI and CABP studies shouldn't be designed and powered with these end points in mind.

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

I don't necessarily think so. Yes, the further out you go, the more difficult it is to differentiate continued antibiotic effects, but I think the clinical response assessment (no matter when it occurs, even at day 4) is in itself just a subjective definition. A patient may not have worsened, but also clearly did not improve, and could still be classified as a success, when these are two entirely different clinical pictures.

Timing of end point assessment

Q What is your opinion on the timing of end-point assessment and what difficulties must be considered when deciding when to assess?

Early end points may be useful for several reasons. At least for CABP and ABSSSI, there appears to be a bit of historic evidence that the antibiotic effect is most pronounced at days 3–4, and thus can be used to justify non-inferiority margins. However, evaluating early end points could also indirectly provide evidence for shorter antimicrobial courses, which then could be tested in independent studies. Overall, I think we treat most infections too long, but just don't have the evidence to suggest doing otherwise. However, one limitation to early end points is that they would not consider any potential for disease relapse, which potentially could be due to the development of resistance. So I believe a later end point is still at least required as a secondary assessment of non-inferiority.

Q What is your opinion on the use of multiple assessments? What cost/ease of implementation implications would this have?

The more assessments that are made, the more corrections for multiple comparisons have to be done on the backend. This certainly complicates interpretation of the study. For ceftaroline, there was reasonably good agreement between different early assessments (and definitions of early assessments) and the subjective test of cure. I don't necessarily see that happening consistently.

This is an area where improved diagnostics and technology are needed to help us identify very simple, objective end points and measure them. Think about how useful it would be to non-invasively measure inocolum at the site of infection and use these continuous data to demonstrate antibiotic effect?

Concluding remarks

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

Drug development is time consuming and challenging. Many of the selective targets for Gram-negatives have already been exploited, which further complicates and delays the development of novel antibiotics. But yes, the additional challenges surrounding regulatory uncertainty have not made bringing new compounds to market any easier. Then again, the majority of new antibiotics recently reviewed have predominantly Gram-positive activity, where we still do have therapeutic options. Hopefully, the ongoing developments in designing appropriate studies combined with the true need for new drugs on the Gram-negative side will permit developers to bring promising agents to market on a faster, simpler course.

Q The need for new antibacterial agents is becoming more urgent – what would you say the vital next steps are in trial design to ensure that much-needed effective treatments are brought to market?

I wish I had the answer to that! It [the situation] is a trifecta, the regulatory system has to come together, there has to be appropriate and good guidance so that pharmaceutical companies know how to design the studies to answer the appropriate questions. For treatments targeting multidrug-resistant Gram-negatives such as *Pseudomonas*, *Acinetobacter* or carbapenemase producing enterobacteriaceae, how are we going to analyze the data? Certainly, there are no good control antibiotics that one can ethically administer to a patient in a blinded manner. Should these then be superiority studies with historical control groups? Should a database be formed? All of these ideas have been proposed.

I think it is a challenging environment, but, basically, the FDA has to be on board, pharmaceutical companies have to be on board, even political policy is on board with the proposed STAAR and GAIN acts. If you think about antibiotics versus any other type of drug class out there, antihypertensives, diabetic drugs and so forth, where a patient is put on one of those drugs and they are on it generally for the rest of their life, unless they don't tolerate it or it stops working, they are chronic illness drugs. Antibiotics are acute illness agents, lots of patients but very short courses, there are no billion-dollar drugs in this arena and, at the end of the day, pharmaceutical companies are businesses, so if it doesn't look like it's worth the investment they may not be very enthusiastic to get in to it. That being said, there are a lot of companies in this area that are working very hard to try and find some of these new compounds and move them along, and now the Infectious Diseases Society of America, NIH, FDA and government as well as the WHO have to certainly make it as easy as possible to get good drugs to the bedside. I think probably infectious disease groups in every country are calling for this. We should all be on the same team, the bacteria are the adversary.

Financial & competing interests disclosure

Joseph Kuti has served as a consultant or member of advisory boards for Astellas US, Inc., Cubist Pharmaceuticals, Inc. and Ortho-McNeil Pharmaceuticals, Inc. He has recieved research grant support from Astellas, Cubist, Merck & Co., Inc. and Pfizer Inc. In addition, he is a member of the speakers bureau for Astellas US, Forest Laboratories, Inc., Merck & Co., Inc. and Ortho-McNeil Pharmaceuticals, Inc. He has no other 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 apart from those disclosed.

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