Title: Setting tuberculosis regimen development on a firm foundation

Patrick PJ Phillips

MRC Clinical Trials Unit at UCL

Aviation House

125 Kingsway

London

WC2B 6NH

Patrick.phillips@ucl.ac.uk

+44 207 670 4637

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Tuberculosis is the leading infectious cause of death worldwide[1]. One of the three pillars of the WHO END-TB strategy is intensified research and innovation, with a focus on the development of new interventions to end the global epidemic[2] - shorter, safer, more effective combination regimens that result in very high cure rates in programme settings and not just in clinical trials. The use of an evidence-based clinical development pathway is essential to ensure that the most effective regimens are quickly identified and advanced into phase III definitive evaluation and while dwindling resources for TB R&D[3] are not wasted on ineffective regimens.

What is often described as the traditional clinical development pathway for TB drug and regimen development – phase IIA evaluating EBA over 14 days, phase IIB evaluating 2-month culture conversion and phase III evaluating relapse – is relatively new. Indeed only the drugs delamanid and bedaquiline and the pretomanid-based regimens have strictly followed this pathway (with the phase III trials for each still ongoing, clinicaltrials.gov identifiers: NCT01424670, NCT02409290, NCT02342886). Historically, the development of regimens for TB did not follow such a formal pathway. This development was largely led and funded by public agencies such as the British MRC[4] or the US Public Health Service[5] with a focus on trials that invariably included 2-3 years of follow-up with a primary outcome of relapse. These trials, that would therefore be described today as phase III trials, were initiated as soon as there was adequate confidence in the bactericidal and sterilizing activities of the individual drugs – the introduction of rifampicin is a case in point[6]. Nevertheless, the bacteriological endpoints included in this meta-analysis (Bonnett et al.) continue to be the cornerstone of evaluating regimens for progression to phase III and this excellent and comprehensive review is timely. While the rank order of regimens is as expected - regimens with isoniazid and rifampicin generally perform better than others on all endpoint studied - this is the first study to systematically examine the available data in this fashion and therefore provides invaluable evidence to support regimen choices and inform future regimen development. However, the heterogeneity and variability of the pooled estimates is striking and begs the question: What now is the role of these endpoints in regimen development?

There were no combination regimens with EBA over 2 or 7 days shown to be greater than that of isoniazid mono-therapy indicating that these endpoints are not useful for comparing regimens. There were fewer regimens evaluated with EBA over 14 days, but the wide confidence intervals again show that this endpoint is likely only to detect very large differences between regimens in the studies that are typically conducted with 15 patients per arm.

Considering the endpoint of percentage culture negative at 8 weeks on solid media, there is very little difference between the results of any of the regimens containing isoniazid, rifampicin and at least one companion drug. Furthermore, the pooled estimate for the standard HRZE regimen is around 90% culture negative at 8 weeks leaving very little room for improvement. A trial with even 80% power to show a difference from 90% to 95% would require 435 patients per arm. The authors themselves conclude that current phase IIA and IIB trials are too small to detect modest differences between regimens in these studies. It is an open question whether modest differences in these phase II endpoints are likely to reflect clinically relevant differences in clinically meaningful endpoints but in any case, what are the alternatives? The authors rightly call for more efficient adaptive screening trial designs to allow more regimens to be evaluated in phase II trials, and sponsors and investigators should also think more broadly about the whole clinical development pathway. This review shows the importance of clinically relevant endpoints in TB trials – endpoints

that measure 'directly how a patient feels, functions or survives'.[7] A key objective in clinical development must be to start studies evaluating relapse as early as is safely possible to select the most promising regimens and reduce the risk of large and expensive phase III failures. Approaches to meet this objective include the use of larger margins of non-inferiority to facilitate smaller and nimbler non-inferiority phase III trials (such as the 12% margin in STAND, NCT02342886), studying a regimen in patients with XDR-TB where there is an even greater need for new treatments, and studying the intended regimen duration prior to phase III (the STEP Phase IIC design[8]).

The authors call for more combinations to be studied across a greater range of Phase II endpoints in order to provide a more precise evaluation of the role of each endpoint in future meta-analyses. While such activities would allow for a better understanding of the role of phase II, this meta-analysis has highlighted the limitations of these endpoints and there will always be a balance between studying more phase II endpoints to fill the data gaps and investing more resources to study clinically-relevant endpoints that will be more useful for comparing regimens.

The authors also highlight the importance of a core outcome set for TB trials and of sharing individual patient data from TB trials. These two activities would facilitate further meta-analyses that allow for systematising knowledge across trials. There are a relatively small number of groups across the world planning and conducting phase II and phase III TB clinical trials and agreement on core outcomes should not be an impossible task with support from projects like the COMET initiative[9]. Similarly, repositories are now available for TB clinical trial data that investigators and sponsors are encouraged to make use of (for example TB-PACTS, http://c-path.org/programs/tb-pacts/), although the resources and expertise required to ensure proper data aggregated and curation and appropriate controlled access should not be under-estimated.[10]

In summary, this well-conducted systematic review provides evidence towards setting tuberculosis regimen development on a firm foundation. Further work is needed as more data become available. In the interim, clinically relevant endpoints must remain the focus of development of new regimens for TB.

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