Tuberculosis 95 (2015) 352–357

Contents lists available at ScienceDirect

Tuberculosis

journal homepage: http://intl.elsevierhealth.com/journals/tube

Innovative clinical trial designs to rationalize TB vaccine development

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ARTICLE INFO

Article history:
Received 20 November 2014
Received in revised form
4 February 2015
Accepted 6 February 2015

Keywords:
Vaccine
Clinical development
Proof of concept
Prevention of infection
Prevention of recurrence
Tuberculosis
Trial design

SUMMARY

A recent trial of a leading tuberculosis (TB) vaccine candidate in 3000 South African infants failed to show protection over that from BCG alone, and highlights the difficulties in clinical development of TB vaccines. Progression of vaccine candidates to efficacy trials against TB disease rests on demonstration of safety and immunogenicity in target populations and protection against challenge in preclinical models, but immunologic correlates of protection are unknown, and animal models may not be predictive of results in humans. Even in populations most heavily affected by TB the sample sizes required for Phase 2b efficacy trials using TB disease as an endpoint are in the thousands. Novel clinical trial models have been developed to evaluate candidate TB vaccines in selected populations using biologically relevant outcomes and innovative statistical approaches. Such proof of concept studies can be used to more rationally select vaccine candidates for advancement to large scale trials against TB disease.

1. Introduction

There were an estimated 9.0 million new cases of tuberculosis (TB) worldwide in 2013, and 1.5 million people died from TB [1]. Although improved diagnostics, directly observed therapy, and improved treatment of HIV have led to a reduction in mortality, drug resistance threatens to undo this progress and raises the specter of a resurgent epidemic [2]. While BCG has been in use for nearly 100 years and is the most widely used vaccine in history, efficacy is variable in children and protection against pulmonary disease in adults, the form that maintains the epidemic, is at best incomplete [3]. The need for a highly effective vaccine against pulmonary TB remains urgent.

Vaccines against *Mycobacterium tuberculosis* (Mtb) have been selected for clinical development based on safety, immune responses, and protection against challenge in pre-clinical animal models. Early clinical trials must then demonstrate safety and immunogenicity, typically first in populations that are not heavily exposed to Mtb and then in target populations who have been BCG vaccinated in infancy, and in whom rates of TB disease can range up to 1% annually. However, even in populations most heavily affected by TB the sample sizes required for Phase 2b efficacy trials are in the thousands, with several years of follow-up needed. For example, in a population with an assumed 1% annual rate of confirmed TB in the placebo group, a vaccine that was 70% effective would require 1540 randomized subjects (770 in each arm) to be followed for 3 years to demonstrate an effect with a two-sided type 1 error of 0.05% and 10% annual loss to follow up. The many challenges in conducting large scale TB vaccine efficacy studies were recently described [4].

Vaccine development is typically iterative, and a vaccine that was 50% effective would also be useful as a platform upon which to build and as a tool to explore correlates of protection. The group sizes required to detect 50% efficacy using the assumptions above or using lower estimates of rates of confirmed TB would be considerably larger. Using a higher error rate is appropriate for proof of concept studies, and would allow for smaller group sizes. However, given a 1% annual incidence in the control group, even with a one-sided error rate of 0.10 and 80% power, ~2000 subjects would need to be followed for three years to determine 50% impact

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http://dx.doi.org/10.1016/j.tube.2015.02.036
1472-9792/

against TB disease. Further, case finding to accurately identify a small number of TB events requires intensive follow-up of study participants, and thorough laboratory evaluation and review of all diagnostic results. Unless correlates of protection were identified and validated, multiple efficacy studies would be required if formulations or antigens for a particular product were modified. The financial and human resources required for such a massive undertaking are daunting.

Development of vaccines against tuberculosis has accelerated dramatically over the past decade, with 14 vaccines currently in clinical trials (Figure 1). One novel vaccine, MVA85A, recently completed an efficacy trial in which ~3000 previously BCG-vaccinated South African infants received one dose of the vaccine at ages 4–6 months and were followed for two years with active and passive TB case detection. There was no protective effect above that seen with BCG alone [5]. Another vaccine, M72, has entered a Phase 2b efficacy trial (clinicaltrials.gov identifier: NCT01755598). Prior to efficacy studies both of these vaccines were evaluated in multiple Phase 1 and 2 trials in various populations, requiring nearly a decade to complete. Several additional candidate vaccines have demonstrated safety and immunogenicity in target populations, and are ready or nearly ready for efficacy studies.

Demonstration of protection against challenge in one or more animal models is one of the current gating criteria for advancement into clinical trials [6]. Typically, challenge studies are conducted in mice and guinea pigs. However, these preclinical models have limitations, as recently reviewed [7]. Dosing, route of administration, and Mtb strains used for challenge all differ significantly from "natural" human infection in the field, which results from airborne exposure to circulating Mtb strains, in many settings with repeated low-level exposures over time. Furthermore, the immune systems, responses to vaccination, and immunopathology in these species differ to varying degrees from those in humans; for example, most strains of mice used in preclinical TB vaccine testing do not form caseating granulomas, the pathologic hallmark of TB in humans. While small animal models remain useful for initial evaluation of candidate vaccines, given the greater similarity between the immune systems of non-human primates and humans, protection against challenge in non-human primates may be more likely to predict efficacy in humans. Novel challenge models are in development, including a guinea pig challenge based on exposure to infectious air from a TB case ward (the "Riley model"), and a BCG or attenuated Mtb challenge in humans [8,9]. Similarly, while cellular immune responses are thought to be required for protection against TB, the specificity, quality and level of response(s) that are likely to be protective are unknown. Demonstrating the ability of any pre-clinical challenge model or immunologic marker to predict human protection ultimately will require validation by vaccine-induced protection against TB disease in a human field trial. Given these factors, the challenge for TB vaccine developers is to rationally, and as efficiently as possible, select candidates to take into human efficacy trials.

TB case accrual rates are the primary driver of size, duration, and cost of clinical efficacy trials. New clinical trial designs are described below that use biologically meaningful endpoints that occur at rates several-fold higher than incident TB disease in selected populations. Impact against these endpoints would help to justify subsequent large scale Phase 2b field trials against TB disease in broader target populations.

2. Prevention of infection

Mtb infection (as opposed to TB disease) is a clinically silent event that is detected by tuberculin skin test (TST) conversion or more recently by an interferon gamma release assay (IGRA), both of which detect cellular memory immune responses to Mtb antigens [10]. Rates of infection as measured using these assays vary depending on the degree of exposure in the population; approximately 30% of close contacts of TB patients develop LTBI ("latent TB infection") and approximately 2 billion people are thought to be

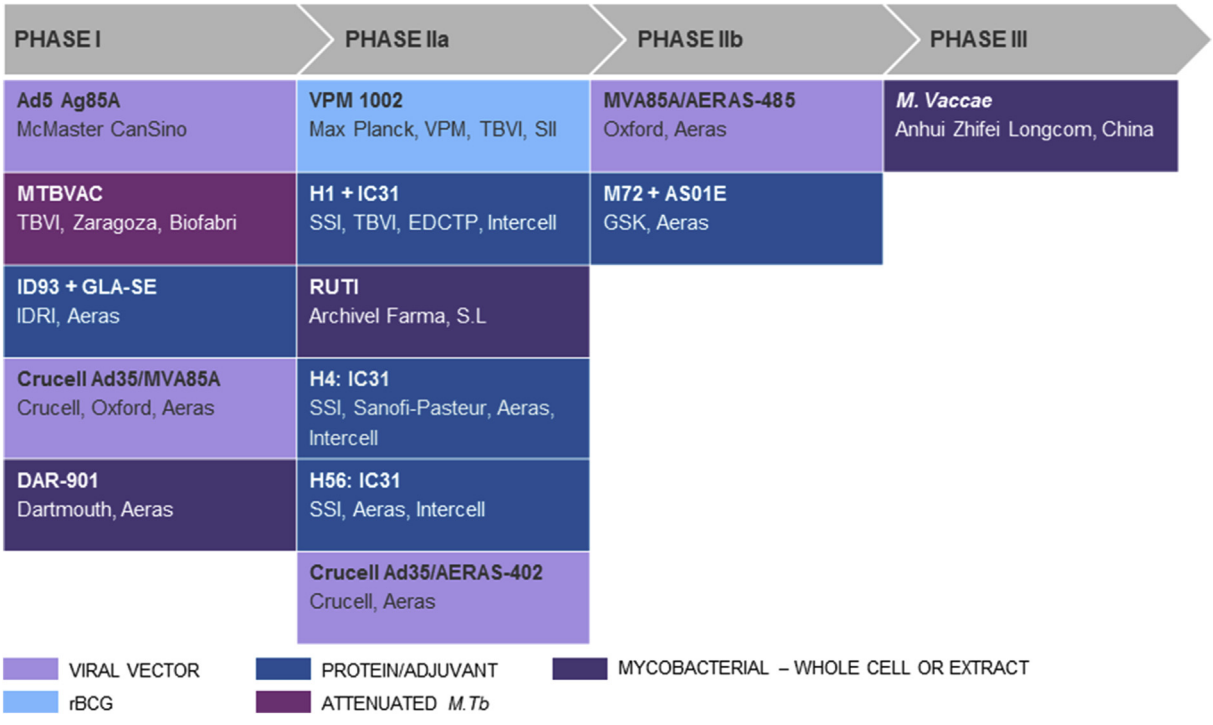

Figure 1. Global clinical pipeline of TB vaccine candidates.