International Journal of Infectious Diseases 32 (2015) 5–12

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Review

Tuberculosis Vaccines – state of the art, and novel approaches to vaccine development

Christopher da Costa *, Barry Walker, Aurelio Bonavia

Aeras, 1405, Research Boulevard, Rockville, MD 20850, USA

ARTICLE INFO

Article history:
Received 19 November 2014
Received in revised form 21 November 2014
Accepted 25 November 2014

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Tuberculosis
Vaccine
Mycobacterium
Vector
Adjuvant

SUMMARY

The quest for a vaccine that could have a major impact in reducing the current global burden of TB disease in humans continues to be extremely challenging. Significant gaps in our knowledge and understanding of the pathogenesis and immunology of tuberculosis continue to undermine efforts to break new ground, and traditional approaches to vaccine development have thus far met with limited success. Existing and novel candidate vaccines are being assessed in the context of their ability to impact the various stages that culminate in disease transmission and an increase in the global burden of disease. Innovative methods of vaccine administration and delivery have provided a fresh stimulus to the search for the elusive vaccine. Here we discuss the current status of preclinical vaccine development, providing insights into alternative approaches to vaccine delivery and promising candidate vaccines. The state of the art of clinical development also is reviewed.

1. Introduction

Despite a 45% reduction in the mortality rate and a 41% reduction in the prevalence rate between 1990 and 2013, tuberculosis remains the second highest cause of death from an infectious disease worldwide. The World Health Organization estimates that in 2013 the global incidence of TB disease was 9 million, with 1.5 million deaths, of which 360,000 were associated with Human Immunodeficiency Virus (HIV) disease.[1] With over a third of the world's population infected with the tubercle bacillus, and an increasing incidence of multi- and extensively drug resistant TB, the sense of urgency to develop a vaccine that could prevent disease transmission remains acute. The *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) vaccine currently being used to prevent TB in infants, despite demonstrated efficacy in reducing the incidence of disseminated and more severe forms of TB, has shown limited effectiveness in prevention of active disease, particularly in older children, adolescents and adults.[2] Mathematical modelling using an age-structured transmission model has recently demonstrated that a vaccine given to adolescents and adults in low- and middle-income countries could have a much larger impact on the burden of TB worldwide and is more likely to be cost-effective than one given only to infants, even if the vaccine has relatively low efficacy and short duration or carries a higher price.[3] A major obstacle to more timely development of an effective vaccine for tuberculosis is the absence of any known correlates of protection. The lack of viable surrogate biomarkers for use in clinical trials of candidate vaccines calls for further research to explore patterns of immune responses associated with latent infection, active disease, and disease recurrence. In this review, the current state-of-the art of preclinical and clinical tuberculosis vaccine development will be reviewed.

2. Preclinical development

2.1. Virus-vectored vaccines

2.1.1. Chimpanzee adenovirus (ChAd) vectors in TB vaccine development

Replication-defective chimpanzee adenovirus vectors are emerging as a promising new class of genetic vaccine carriers. Adenovirus vectors are a strong choice for tuberculosis (TB) vaccine delivery since they are natural respiratory viruses and can target the lung where Mycobacterium tuberculosis (MTB)

* Corresponding author. Aeras, 1405 Research Boulevard, Rockville, MD 20850, USA. Tel.: +1 301-547-2900; fax: +1 301-547-2901.
E-mail addresses: chrisdacosta26@gmail.com (C. da Costa), bwalker@aeras.org (B. Walker), abonavia@aeras.org (A. Bonavia).

http://dx.doi.org/10.1016/j.ijid.2014.11.026

primarily resides. Adenoviruses can express multiple antigens at a time, have an intrinsic adjuvant effect and an acceptable safety margin. Adenoviruses can also elicit both strong humoral and cell mediated responses. However, clinical use of human adenoviruses as a vaccine platform has been limited by the fact that most of the population presents pre-existing immunity and this limits the efficacy of this virus-vectored vaccine. Termination of the adenovirus type 5 (Ad5) HIV-1 vaccine clinical trial (STEP trial) in 2007, due to a lack of demonstrable positive impact on virus acquisition or virus load following infection, and the observed increased rate of HIV infection in vaccine recipients who had prior immunity to Ad5 and/or were circumcised, led to a decline in enthusiasm for Ad5-vectored vaccine development. ChAds have emerged as an alternative since humans present none or low levels of neutralizing antibodies. Although from a different species, ChAds can infect humans with a respiratory tract tropism. ChAd vectors have now reached the clinical development stage and have been shown to be capable of inducing immune responses against encoded antigens, with added advantages of a good safety profile and ease of large-scale manufacturing.[4] Further preclinical development of a replication-deficient chimpanzee adenovirus-vectored TB vaccine is currently in progress, including a Phase 1 trial to evaluate the safety and immunogenicity of a ChAd-Ag85A (ChAdOx1 85A) priming vaccine with and without an MVA85A boost in healthy adults (http://clinicaltrials.gov/ct2/show/NCT01829490).

2.1.2. Mucosal delivery of virus-vectored vaccines

BCG vaccination has been classically delivered intradermally. However, the best route of administration for a TB vaccine still needs to be elucidated. Evidence from mouse studies using different viral vectors with Ag85A comparing mucosal and parenteral vaccination supports that targeting the respiratory tract upon delivery has a benefit in protection against TB.[5,6] Similarly, vaccination with BCG via aerosol or intranasally also confers greater protection than subcutaneous (s.c.) or intradermal (i.d.) administration in mice or guinea pigs.[7–9] Published data suggest that vaccination via the respiratory tract triggers and sustains resident effector cells in the lung that may control the infection. Mucosal delivery by aerosol administration has been tested in non-human primates; aerosolized MVA-Ag85 given as a boost to BCG primed rhesus macaques has been shown to elicit a strong polyfunctional CD4+ T cell response in the lung measured by PPD stimulation in BAL.[10] The CD8+ response in the same context was weak, which suggests that a heterologous boost with a different delivery platform would be needed to complement the MVA vaccination. This is the first study to show a recombinant MVA-vectored vaccine to be highly immunogenic when delivered by the aerosol route to nonhuman primates. The results also provided important safety and proof-of-concept data for further evaluation of the aerosol route of immunization for use in human clinical trials. Evaluation of an aerosolized preclinical candidate Aeras402 (Crucell Ad35/Aeras 402-Ag85A/Ag85B/10.4) in rhesus macaques has shown strong immunogenicity.[11,12] In these experiments, in the BAL fluid the antigen specific cytokine-producing memory T cell CD4+ subset reached 3-12% while the CD8+ subset reached 20-50%. Both responses were sustained for 10 weeks. In the first immunogenicity experiment the aerosol route of administration was compared to intramuscular (i.m.) delivery clearly showing that the parenteral vaccination could not elicit effector T cells in the BAL fluid. However despite such notable immune responses being observed in the lungs, this was not reflected in reduced bacterial load, nor in increased survival overall upon MTB challenge. It is important to note that rhesus macaques are highly susceptible to MTB infection and even BCG is not efficiently protective.[13] In this experiment an unusually high dose of MTB Erdman (275 CFUs) was used and yet the control groups did not behave as expected (naïve group did not exhibit high mortality and BCG failed to protect when compared to naïve group). Further repeat of this experiment is needed to draw a clear conclusion and understand whether the choice of vector or antigens is related to the lack of biological activity observed. Aeras, in collaboration with the National Institutes of Health Vaccine Research Center (NIH-VRC, Bethesda, MD) and the University of Pittsburgh (Pittsburgh, PA), are currently evaluating Ad5 constructs with antigen cassettes that include MTb39a/MTb32a or ESAT6/Ag85B. These vaccines have yielded strong immunogenicity in preliminary experiments in non-human primates (Dr. Robert Seder and Dr. JoAnne Flynn, personal communication).

The use of dry powder formulations could offer practical advantages over needle delivery in the field, easing compliance and simplifying the technical operations of single use devices, storage, and potentially eliminating a cold chain requirement. Aerosol vaccination has been tested in measles and the results have been encouraging, however immunogenicity and protection has been quite heterogeneous when compared with s.c. delivery and was also dependent on the subject age.[14,15] Due to the differences in pathogenesis and the mechanism of protection, the aerosolization of a TB vaccine needs to be rigorously investigated and remains an attractive strategy.

2.1.3. Cytomegalovirus as a TB vaccine vector

Rhesus cytomegalovirus (RhCMV) vectors expressing SIV antigen have been shown to control the infection of highly pathogenic SIVMAC239 in rhesus macaques.[16] Vaccine protection can be partly attributed to the establishment of persistence of such vectors in the macaques and continual high expression of antigens. Furthermore, the discovery that CMV can elicit high levels of prolonged non-conventional CD8+ T cells that recognize unusual, diverse and highly promiscuous epitopes and also elicit CD4+ responses[17,18] makes it a very attractive platform for a TB vaccine. Currently Aeras, in collaboration with Oregon Health & Science University (Portland, OR), are investigating the feasibility of this platform in non-human primates using several RhCMV vectors expressing the MTB antigens Ag85A/85B, ESAT6, Rv3407, Rv1733c, Rv2626c and RPF A/C/D with very encouraging preliminary results in terms of immunogenicity and protection (Dr. Louis J Picker, personal communication).

2.2. Electroporated DNA vaccination: a promising new technique for TB

Recent advances in DNA vaccine delivery techniques have renewed interest in developing a safe and effective DNA vaccine for TB. Animal studies in mice using conventional delivery techniques have previously shown promising results, however immunogenicity has been modest at best.[19,20] Despite this, animal studies have clearly demonstrated the induction of both CD4+ and CD8+ T-cell responses directed against mycobacterial antigens.[21,22] Numerous mycobacterial antigens (including Ag85A, Ag85B, MPT64, ESAT-6, PE/PPEs, Rv2031c, and Rv3846) have been tested in candidate vaccines in mice and guinea pig with mixed efficacy results.[23–26] More recently, the technique of electroporation (EP) has been used as a method of enhancing the delivery of DNA vaccines in animal models of a wide variety of infectious diseases, including TB, with dose sparing in the range of 1000-fold compared to the administration of naked plasmid DNA.[27] Potential benefits of such an approach also include a broad-based immune response, both cellular and humoral,[28] reduced rates of vaccine-induced side effects such as headache, fever, and transient pain.[29] In addition, DNA vaccines can be readily manufactured on a large scale.[30]