28 September 2018

Candidate tuberculosis (TB) vaccine can prevent active pulmonary TB in HIV-negative adults in phase II study

Primary analysis published in the *New England Journal of Medicine* shows positive results in clinical trial conducted in tuberculosis endemic regions

The ***New England Journal of Medicine*** this week published the primary results of an ongoing phase IIb clinical trial testing the candidate tuberculosis vaccine M72/AS01E. This analysis shows that M72/AS01E significantly reduced the incidence of pulmonary tuberculosis disease in HIV-negative adults who were already infected with latent TB at the time of vaccination. The results demonstrate an overall vaccine efficacy of 54%, with varied response rates observed in different demographic sub-groups. The candidate vaccine had an acceptable safety and reactogenicity profile.

The South African Tuberculosis Vaccine Initiative (SATVI) and the Wellcome Centre for Infectious Diseases Research in Africa (CIDRI-Africa), tuberculosis research groups based in the Institute of Infectious Disease & Molecular Medicine at the University of Cape Town, are two of 11 sites in Kenya, South Africa and Zambia where the study is conducted. The study is sponsored by the global healthcare company GSK, and conducted in partnership with Aeras, a non-profit organization dedicated to developing vaccines against tuberculosis.

Tuberculosis is the leading cause of death through infectious disease worldwide and represents a significant public health threat with 1.6 million attributed deaths in 2016 globally. In South Africa, the estimated incidence of tuberculosis is 781 per 100,000 of the population. The World Health Organization estimates that one-quarter of the global population has latent tuberculosis, with increasing prevalence of multi-drug resistant strains. Currently, there is no available tuberculosis vaccine with proven, consistent efficacy in adult populations.

“These results are a major advance for TB vaccine development, showing for the first time that a protein subunit vaccine can prevent progression to active TB disease in people who are already infected with latent TB at the time of vaccination,” says Professor Mark Hatherill.

“We are thrilled that a new generation TB vaccine candidate can prevent progression to active TB disease. This study lays the foundation for the next step, which is to determine what this protective immune response looks like so that we can improve TB vaccines even further,” said Associate Professor Thomas Scriba.

Professor Robert J Wilkinson of CIDRI-Africa, Imperial College and the Francis Crick Institute London commented: “We are pleased to have had a large part in the conduct and analysis of this study. The results are intriguing and, overall, highly encouraging. A major task now will be to analyse samples collected from the trial to look for clues how we might do even better. Our previous experience and the combination of Crick and the Wellcome Centre in Cape Town uniquely positions us to play a significant role in this effort, at the same time as contributing to the development of scientific careers in Africa.”

The study assesses the safety and efficacy of M72/AS01E, in adults with latent tuberculosis infection, against development of pulmonary tuberculosis disease. The ongoing trial is conducted in tuberculosis-endemic regions in Kenya, South Africa and Zambia and involves 3,573 HIV-negative adults. For this analysis, participants who received two doses of either M72/AS01E or placebo 30 days apart have been followed for at least 2 years to detect evidence of pulmonary tuberculosis disease.

Ten participants who received the vaccine developed active pulmonary tuberculosis compared to 22 participants in the placebo group.

The study is still ongoing and a final analysis including all efficacy, safety, reactogenicity and immunogenicity data will be performed in 2019 after all participants have completed three years of follow up.

About the study

This study is a Phase IIb, multicentre, randomized (ratio 1:1), double-blind, placebo-controlled study with 2 groups: M72/AS01E or placebo. The study is conducted in tuberculosis endemic regions, at 11 sites in South Africa, Zambia and Kenya. (www.clinicaltrials.gov NCT01755598)

The primary objective of the study is to investigate if two doses of the M72/AS01E candidate vaccine can prevent adults with latent tuberculosis infection from developing pulmonary tuberculosis disease, compared to people who receive placebo. The study also evaluates the safety, reactogenicity and immunogenicity of the M72/AS01E candidate vaccine.

Nearly all participants (99%) in the study consented to enter into a bio-banking study. The samples collected during this study will allow researchers to further investigate the potential vaccine-induced correlates of protection against tuberculosis and attempt to identify markers that indicate those at high risk of developing pulmonary tuberculosis disease. (www.clinicaltrials.gov NCT02097095).

The study is sponsored by GSK and conducted in partnership with Aeras. Funders include the Bill & Melinda Gates Foundation, the United Kingdom’s Department for International Development, the Directorate General for International Cooperation in the Netherlands, and the Australian Agency for International Development.

About the candidate vaccine

M72/AS01E candidate vaccine contains the M72 recombinant fusion protein derived from two *Mycobacterium tuberculosis* antigens (Mtb32A and Mtb39A), combined with the Adjuvant System AS01, which is also a component of the GSK's RTS,S/AS01 and Shingrix vaccines.
Primary results showed M72/AS01E to have an acceptable safety and reactogenicity profile. Solicited and unsolicited adverse events within 7 days post-injection were more frequent among M72/AS01E recipients (91.2%) than placebo recipients (68.9%), the difference attributed mainly to injection site reactions and flu-like symptoms. Serious adverse events, potential immune-mediated diseases and deaths all occurred with similar low frequencies between groups. The fatalities encountered amongst the participants in this study were unrelated to the administration of the candidate vaccine or placebo.

About tuberculosis

One-quarter of the global population is estimated to be infected with latent TB and tuberculosis is the leading infectious cause of death worldwide. There were an estimated 10.4 million new tuberculosis cases and 1.7 million deaths attributed to tuberculosis in 2016. After the initial infection with latent TB, the disease – if untreated – often progresses to involve large parts of the lung causing pulmonary tuberculosis, which is responsible for the majority of fatalities caused by tuberculosis. An effective vaccine against tuberculosis would have a marked impact on tuberculosis control, including drug-resistant tuberculosis, through interruption of transmission; and would help achieve the WHO target of ending the tuberculosis epidemic by 2035.

About SATVI

The South African Tuberculosis Vaccine Initiative is a research group based at the University of Cape Town and with a field site in the town of Worcester, Western Cape, that focuses on understanding risk for and protection against tuberculosis, in order to develop a new safe and effective TB vaccine.
http://www.satvi.uct.ac.za

About CIDRI-Africa

The Wellcome Centre for Infectious Diseases Research in Africa fosters investigator-led approaches via the overarching scientific objective of combatting infection, especially HIV-1 and tuberculosis, through clinical and laboratory research. Three interlinked platforms support clinical studies in the community, improve the depth of laboratory investigations for infected materials, and advance cutting-edge integration of high-dimensional, big data.
http://www.cidri-africa.uct.ac.za

Ends

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