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IMMUNOLOGICAL ASPECTS

Safety and immunogenicity of the M72/AS01$_E$ candidate tuberculosis vaccine in adults with tuberculosis: A phase II randomised study

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SUMMARY

Previous studies have shown that the M72/AS01$_E$ candidate tuberculosis vaccine is immunogenic with a clinically acceptable safety profile in healthy and *Mycobacterium tuberculosis*-infected adults. This phase II, observer-blind, randomised study compared the safety, reactogenicity, and immunogenicity of M72/AS01$_E$ in 3 cohorts: tuberculosis-naïve adults (n = 80), adults previously treated for tuberculosis (n = 49), and adults who have completed the intensive phase of tuberculosis treatment (n = 13).

In each cohort, 18–59-year-old adults were randomised (1:1) to receive two doses of M72/AS01$_E$ (n = 71) or placebo (n = 71) and followed-up until six months post-dose 2. Safety and reactogenicity were assessed as primary objective.

Recruitment in the study ended prematurely because of a high incidence of large injection site redness/swelling reactions in M72/AS01$_E$-vaccinated adults undergoing tuberculosis treatment. No additional clinically relevant adverse events were observed, except one possibly vaccine-related serious adverse event (hypersensitivity in a tuberculosis-treated-M72/AS01$_E$ participant). Robust and persistent M72-specific humoral and polyfunctional CD4$^+$ T-cell-mediated immune responses were observed post-M72/AS01$_E$ vaccination in each cohort. In conclusion, the M72/AS01$_E$ vaccine was immunogenic in adults previously or currently treated for tuberculosis, but further analyses are needed to explain the high local reactogenicity in adults undergoing tuberculosis treatment.

ClinicalTrials.gov: NCT01424501

1. Introduction

Tuberculosis (TB) remains one of the world's deadliest communicable diseases. It has been estimated that one third of the world population is infected with *Mycobacterium tuberculosis*, resulting in approximately 9.6 million new cases and 1.5 million deaths in 2014 [1]. Infected individuals can be clinically classified into patients with active TB disease and individuals with latent TB infections (in the absence of clinical symptoms of disease) [2–5]. Latent TB infections include a spectrum of individuals at widely differing risk of developing active TB [6]._ENREF_2 The vast majority of individuals with latent TB infections never develop active disease and remain asymptomatic, but that group acts as a reservoir for new cases. Moreover, it can take months to years to develop symptomatic and bacteriologically detectable TB. During this period, asymptomatic states with manifestations and duration dependent on the host immune response remain mostly unidentified.

The Bacille Calmette-Guérin (BCG) is the only licensed TB vaccine, but varying estimates of its efficacy in preventing pulmonary

Abbreviations: AE, adverse event; ATP, according to protocol; BCG, Bacille Calmette-Guérin; CFP10, culture filtrate protein-10; CI, confidence interval; CMI, cell-mediated immunity; ELISA, enzyme linked immunosorbent assay; EU/mL, ELISA units per millilitre; GMC, geometric mean concentration; HIV, human immunodeficiency virus; ICS, intracellular cytokine staining; IFN-γ, interferon-gamma; IL, interleukin; MedDRA, medical dictionary for regulatory activities; PBMC, peripheral blood mononuclear cell; PPD, purified protein derivative; SAE, serious adverse event; SAS, statistical analysis system; TB, tuberculosis; TNF-α, tumour necrosis factor-alpha; TVC, total vaccinated cohort.

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TB disease have been found in clinical trials [7]. Therefore, several prophylactic and immunotherapeutic vaccines against TB disease are under development, including the prophylactic M72/AS01$_E$ vaccine [8,9]. The M72/AS01$_E$ vaccine is composed of the M72 antigen, which is a recombinant fusion protein derived from the *M. tuberculosis* proteins Mtb32A and Mtb39A, and the AS01 Adjuvant System [10]. Previous studies have shown that this vaccine has a clinically acceptable safety profile, and induces humoral immune responses and cell-mediated immunity (CMI) in healthy, human immunodeficiency virus (HIV)-infected and *M. tuberculosis*-infected adults, and in BCG-vaccinated toddlers [10–15].

In this study, we compared for the first time the safety, reactogenicity, and immunogenicity of M72/AS01$_E$ in adults currently receiving treatment for TB disease and adults with previous history of successfully treated pulmonary TB disease. Adults receiving treatment for TB disease, who had completed the intensive phase of treatment, were included in this study as a surrogate for individuals with latent TB evolving to active but still undiagnosed overt TB disease who are hence not yet treated for TB. Even if the tools were available to identify patients with latent TB evolving to active TB disease, it is unlikely that these patients would be included in prophylactic clinical trial settings, as once identified and diagnosed, patients with active TB should be offered antibiotic treatment. Although effective TB vaccines are not available currently, if such vaccines are included in national immunisation programmes in the future, patients with latent TB evolving to active TB disease could inadvertently be vaccinated and hence pose a theoretical safety concern. Adults with a history of active TB disease who received previous treatment were also included in the present study as they represent a group of patients at risk of relapse due to re-infection or reactivation, who would greatly benefit from a vaccine against TB [16].

2. Methodology

2.1. Study design and ethics

This was a phase II, observer-blind, randomised, controlled study conducted initially in four centres in Taiwan and subsequently in two centres in Estonia. In Taiwan, participants were enrolled through the National Taiwan University Hospital (NTUH) and other affiliated institutions. The NTUH is the biggest medical centre in Taiwan and conducts over 150 clinical trials per year. In Estonia, participants were enrolled through the Innomedica OÜ centre in Tallin and through Tartu University Hospital Lung Clinic. The study started on November 14, 2011. However, following the identification of a safety signal, enrolment and further vaccination were terminated by the Sponsor on December 16, 2013. All the enrolled participants continued the study until the end, and the last visit occurred on April 10, 2014.

The study included three cohorts: adults with smear- or culture-confirmed pulmonary TB disease who had completed the intensive phase of treatment, i.e. had documented treatment for pulmonary TB disease ongoing for 2–4 months prior to vaccination (TB-treatment cohort); adults with previous history of successfully treated pulmonary TB disease at least one year prior to vaccination and with no active pulmonary disease on chest X-ray (TB-treated cohort); and adults who had no active pulmonary disease as indicated by chest X-ray, no signs and symptoms of TB disease, and no history of chemoprophylaxis or treatment for TB (TB-naïve cohort). Chest radiographs were performed for all participants before the first vaccination. For the participants from the TB-naïve cohort, a Mantoux test (tuberculin purified protein derivative (PPD) RT 23 SSI; Statens Serum Institute, Copenhagen, Denmark) was performed at least 2 weeks before first vaccination.

Participants from each cohort were randomised (1:1) using a block randomisation (MATEX; SAS Institute Inc.) in two parallel groups to receive two doses of the M72/AS01$_E$ vaccine or a placebo. The treatment allocation at the investigator sites was performed using a central Randomisation System on Internet (SBIR, GSK Vaccines) with a minimisation algorithm. The first dose of vaccine was administered to a safety subset of 12 participants in the TB-treated cohort. The vaccination continued in the TB-treated cohort and started in the TB-treatment cohort if no safety issues were observed during the protocol-defined review of data that was performed on the safety subset after the first vaccination. The same process was repeated after the second vaccine dose administration. Further enrolment and vaccination would be stopped if the following holding rules were met: i) vaccination in a particular cohort would be put on hold pending review of data if at least two vaccinated participants in that cohort were withdrawn for a vaccine-related adverse event (AE) by the investigator during the safety review time period, and ii) vaccination in all cohorts would be put on hold pending review of data for a fatal or life-threatening serious AE (SAE) judged by the investigator to be related to vaccination at any time during the study, or for an anaphylactic shock reaction following vaccination. For participants in the TB-naïve cohort, vaccination proceeded without any scheduled safety review.

The study protocol and informed consent forms were reviewed and approved prior to initiation of the study by national Ethics Committees in Taiwan and subsequently in Estonia. Written informed consent was obtained from each participant prior to enrolment. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The trial was registered with ClinicalTrials.gov (NCT01424501). A summary of the protocol is available at http://www.gsk-clinicalstudyregister.com (GSK study ID 114886).

2.2. Study population and vaccination

Study participants were adults aged 18–59 years at first vaccination, who were seronegative for HIV-1 and HIV-2 antibodies, had no history of extra-pulmonary TB, and had provided written informed consent. Participants in the TB-treatment cohort had documented treatment for pulmonary TB ongoing for 2–4 months prior to vaccination, were enrolled after their first check-up visit following the active phase of treatment, and received TB treatment independently of the study (by the TB centre recruiting the participants or through referral to a TB centre). In both countries, the World Health Organisation guidelines on the treatment of TB were followed, and regimens that included isoniazid, rifampicin, ethambutol and pyrazinamide were used for at least 2 months in the intensive phase of the disease, followed by isoniazid, rifampicin and ethambutol in the continuous phase for 4 months [17]. Participants who had successfully completed treatment for TB disease at least 1 year before the first vaccination were enrolled in the TB-treated cohort.

Participants were excluded if they had used an investigational product within 30 days prior to the study or planned to use an investigational product during the study, had a history of administration of experimental TB vaccines, were immunosuppressed (chronic administration of immunosuppressants or other immune-modifying drugs within 6 months prior to the first vaccine dose, or any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination), had received immunoglobulins or blood products within 3 months before administration of the first dose of the study vaccine or had planned administration during the study, or had any chronic drug therapy that had to be continued during the study period and

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