Safety and immunogenicity of a chimpanzee adenovirus-vectored Ebola vaccine in healthy adults: a randomised, double-blind, placebo-controlled, dose-finding, phase 1/2a study

Olga De Santis, Régine Audran, Emilie Pothin, Loane Warpelin-Decrausaz, Laure Vallotton, Grégoire Wuerzner, Camille Cochet, Daniel Estoppey, Viviane Steiner-Monard, Sophie Lonchampt, Anne-Christine Thierry, Carole Mayor, Robert T Bailer, Olivier Tshiani Mbaya, Yan Zhou, Aurélie Ploquin, Nancy J Sullivan, Barney S Graham, François Roman, Iris De Ryck, W Ripley Ballou, Marie Paule Kieny, Vasee Moorthy, François Spertini, Blaise Genton

Summary

Background The ongoing Ebola outbreak led to accelerated efforts to test vaccine candidates. On the basis of a request by WHO, we aimed to assess the safety and immunogenicity of the monovalent, recombinant, chimpanzee adenovirus type-3 vector-based Ebola Zaire vaccine (ChAd3-EBO-Z).

Methods We did this randomised, double-blind, placebo-controlled, dose-finding, phase 1/2a trial at the Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland. Participants (aged 18–65 years) were randomly assigned (2:2:1), via two computer-generated randomisation lists for individuals potentially deployed in endemic areas and those not deployed, to receive a single intramuscular dose of high-dose vaccine (5×10^{10} viral particles), low-dose vaccine ($2\cdot5\times10^{10}$ viral particles), or placebo. Deployed participants were allocated to only the vaccine groups. Group allocation was concealed from non-deployed participants, investigators, and outcome assessors. The safety evaluation was not masked for potentially deployed participants, who were therefore not included in the safety analysis for comparison between the vaccine doses and placebo, but were pooled with the non-deployed group to compare immunogenicity. The main objectives were safety and immunogenicity of ChAd3-EBO-Z. We did analysis by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT02289027.

Findings Between Oct 24, 2014, and June 22, 2015, we randomly assigned 120 participants, of whom 18 (15%) were potentially deployed and 102 (85%) were non-deployed, to receive high-dose vaccine (n=49), low-dose vaccine (n=51), or placebo (n=20). Participants were followed up for 6 months. No vaccine-related serious adverse events were reported. We recorded local adverse events in 30 (75%) of 40 participants in the high-dose group, 33 (79%) of 42 participants in the low-dose group, and five (25%) of 20 participants in the placebo group. Fatigue or malaise was the most common systemic adverse event, reported in 25 (62%) participants in the high-dose group, 25 (60%) participants in the low-dose group, and five (25%) participants in the placebo group, followed by headache, reported in 23 (57%), 25 (60%), and three (15%) participants, respectively. Fever occurred 24 h after injection in 12 (30%) participants in the high-dose group and 11 (26%) participants in the low-dose group versus one (5%) participant in the placebo group. Geometric mean concentrations of IgG antibodies against Ebola glycoprotein peaked on day 28 at 51 μg/mL (95% CI 41·1–63·3) in the high-dose group, 44·9 μg/mL (25·8–56·3) in the low-dose group, and 5·2 μg/mL (3·5–7·6) in the placebo group, with respective response rates of 96% (95% CI 85·7–99·5), 96% (86·5–99·5), and 5% (0·1–24·9). Geometric mean concentrations decreased by day 180 to 25·5 μg/mL (95% CI 20·6–31·5) in the high-dose group, 22·1 μg/mL (19·3–28·6) in the low-dose group, and 3·2 μg/mL (2·4–4·9) in the placebo group. 28 (57%) participants given high-dose vaccine and 31 (61%) participants given low-dose vaccine developed glycoprotein-specific CD4 cell responses, and 33 (67%) and 35 (69%), respectively, developed CD8 responses.

Interpretation ChAd3-EBO-Z was safe and well tolerated, although mild to moderate systemic adverse events were common. A single dose was immunogenic in almost all vaccine recipients. Antibody responses were still significantly present at 6 months. There was no significant difference between doses for safety and immunogenicity outcomes. This acceptable safety profile provides a reliable basis to proceed with phase 2 and phase 3 efficacy trials in Africa.

Funding Swiss State Secretariat for Education, Research and Innovation (SERI), through the EU Horizon 2020 Research and Innovation Programme.

Lancet Infect Dis 2016; 16: 311–20

Published Online December 22, 2015 http://dx.doi.org/10.1016/S1473-3099(15)00486-7

See Comment page 267

Policlinique Médicale Universitaire, Lausanne, Switzerland (O De Santis MRes, C Cochet MD, D Estoppey MD, S Lonchampt MSc, Prof B Genton MD); **Division of Immunology and Allergy** (R Audran PhD, V Steiner-Monard MD, A-C Thierry BS, C Mayor BS, F Spertini MD), **Clinical Trial Unit** (L Warpelin-Decrausaz PhD, L Vallotton MD, G Wuerzner MD), **and Infectious Diseases Service, Department of Medicine** (Prof B Genton), **Lausanne University Hospital, Switzerland; Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland** (E Pothin PhD, Prof B Genton); **Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA** (R T Bailer PhD, O T Mbaya MD, Y Zhou PhD, A Ploquin PhD, N J Sullivan PhD, B S Graham MD); **GSK Vaccines, Rixensart, Belgium** (F Roman MD, I De Ryck MD, W R Ballou MD); **and WHO, Geneva, Switzerland** (M P Kieny PhD, V Moorthy MD)

Correspondence to: Olga De Santis, Policlinique Médicale Universitaire, Lausanne 1011, Switzerland **olga.de-santis@hospvd.ch**

Introduction

Ebola virus causes a severe, often fatal, illness, and several outbreaks have occurred since the virus was first reported in 1976. The largest recorded outbreak of Ebola virus disease is ongoing, and more than 28 000 cases and more than 11 000 deaths in three countries in west Africa had been reported by September, 2015.[1] WHO has declared the current outbreak an international public health emergency.

Research in context

Evidence before this study

We searched PubMed for clinical trials up to Aug 17, 2015, with the search terms "Ebola" AND "vaccine", with no language or date restrictions. Two DNA vaccines and one recombinant adenovirus serotype 5 using different versions of the Ebola virus or Marburg virus glycoprotein protein have been tested in the past 10 years. Chimpanzee adenovirus 3 (ChAd3)-vectored vaccines using monovalent and bivalent formulations of the Ebola virus glycoprotein were tested in late 2014 in US and UK phase 1 clinical trials with small sample sizes. A recombinant vesicular stomatitis virus (rVSV)-vectored Ebola vaccine was simultaneously tested in a multisite phase 1 trial. More recently, investigators of a phase 1 trial in China used a recombinant adenovirus serotype 5 vector-based Ebola vaccine expressing the glycoprotein of the 2014 epidemic strain. No safety issues arose from these trials, except for cases of arthritis and rash with rVSV, mainly reported at one site. All these trials done simultaneously to ours were published as preliminary reports including safety and immunogenicity data up to day 28 after injection.

Added value of this study

Our study provides the most comprehensive results of a phase 1/2 trial with ChAd3 vector-based vaccine expressing the Ebola virus glycoprotein. This trial was the only one that was placebo-controlled, allowing for the most accurate assessment of safety and reactogenicity. Among all Ebola vaccine trials, this is the only one that provides safety and immunogenicity results up to 6 months after injection, which provides some insight into the value of the vaccine over the course of an epidemic. No safety signal was recorded in our trial. All vaccine recipients had humoral immune responses that peaked at day 28, and then decreased by about half 6 months after injection. Interferon-γ mononuclear cell responses were still present at that time.

Implications of all the available evidence

When compared with results of the rVSV-vectored Ebola vaccine at 2×10^7 or 5×10^7 plaque-forming units, we can conclude that the safety profile of the ChAd3 Ebola vaccine (ChAd3-EBO-Z) at doses of 10^{10} viral particles is slightly better, but the humoral responses slightly lower, 1 month after injection. In view of the good safety profile of ChAd3-EBO-Z at doses of 10^{10} viral particles in the present trial, the 10^{11} viral particle dose would seem appropriate to use when proceeding to phase 2 and 3 trials in Africa as planned, especially because the few available safety data with ChAd3-EBO-Z at 10^{11} viral particles show an acceptable adverse events profile and, more importantly, similar antibody responses, as those obtained with the 2×10^7 plaque-forming units dose of the rVSV-vectored vaccine. Assuming that the anti-glycoprotein antibody concentration is correlated with protection (even if the antibodies are not themselves protective), the promising efficacy results reported in the preliminary report of the rVSV-vectored vaccine in the phase 3 trial in Guinea could also be obtained with the ChAd3-EBO-Z vaccine at a dose of 10^{11} viral particles. The persistence of antibodies at month 6, although at a reduced concentration, might suggest that some protection remains. However, this theory needs to be confirmed in a thorough phase 3 trial. Detailed correlation of immunological data and protection in non-human primate studies might also give some insight into efficacy, if a phase 3 trial becomes impossible to do because of an insufficient number of new cases of Ebola virus disease.

As a result of large multilateral public health interventions, the case incidence of Ebola virus disease had declined to less than ten cases per week by the end of July, 2015; however, no approved treatment or vaccine is yet available.

Current efforts to develop a vaccine are focused on the viral glycoprotein encoded by the virus. The most advanced vaccine candidates tested so far are based on the glycoprotein from either the Zaire strain of Ebola virus (responsible for the current outbreak) or the Sudan strain. Candidates in which viral glycoprotein is expressed in either chimpanzee adenovirus, human adenovirus, or vesicular stomatitis virus have shown promise in non-human primate models of Ebola virus disease, and in initial clinical trials.[2–7] Moreover, preliminary results of a phase 3 clinical trial with the replication-competent recombinant vesicular stomatitis virus (rVSV)-vectored vaccine showed encouraging efficacy results in Guinea.[8,9]

Rationale for development of this vaccine is based on previous human experience with other investigational filovirus vaccines and the development of non-human adenovirus vectors with low seroprevalence in human beings.[3,10–14] Previous phase 1 clinical trials investigated the bivalent and monovalent vaccines encoding wild-type glycoprotein from Zaire and Sudan species of Ebola virus[4] or Zaire species only.[15] In response to a request from WHO in September, 2014, we undertook the present study to assess the safety and immunogenicity of the monovalent, recombinant, chimpanzee adenovirus type-3 vector-based Ebola Zaire (ChAd3-EBO-Z) vaccine construct. We aimed to build on and extend the clinical development plan for a chimpanzee adenovirus 3 (ChAd3)-vectored vaccine encoding Ebola glycoproteins that has been developed by the US National Institutes of Health in collaboration with GSK–Okairos, WHO, and the University of Oxford.

Methods

Study design and participants

We did this randomised, double-blind, placebo-controlled, dose-finding, phase 1/2a study at the Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland.