UKE Paper of the Month April 2020

Safety and immunogenicity of a modified vaccinia virus Ankara vector vaccine candidate for Middle East respiratory syndrome: an open-label, phase 1 trial

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Lancet Infect Dis.pii: S1473-3099(20)30248-6.

ABSTRACT:

Background The Middle East respiratory syndrome coronavirus (MERS-CoV) causes a respiratory disease with a case fatality rate of up to 35%. Given its potential to cause a public health emergency and the absence of efficacious drugs or vaccines, MERS is one of the WHO priority diseases warranting urgent research and development of countermeasures. We aimed to assess safety and tolerability of an anti-MERS-CoV modified vaccinia virus Ankara (MVA)-based vaccine candidate that expresses the MERS-CoV spike glycoprotein, MVA-MERS-S, in healthy adults.

Methods This open-label, phase 1 trial was done at the University Medical Center Hamburg-Eppendorf (Hamburg, Germany). Participants were healthy men and women aged 18–55 years with no clinically significant health problems as determined during medical history and physical examination, a body-mass index of 18·5–30·0 kg/m² and weight of more than 50 kg at screening, and a negative pregnancy test for women. A key exclusion criterion was a previous MVA vaccination. For the prime immunisation, participants received doses of 1×10^7 plaque-forming unit (PFU; low-dose group) or 1×10^8 PFU (high-dose group) MVA-MERS-S intramuscularly. A second identical dose was administered intramuscularly as a booster immunisation 28 days after first injection. As a control group for immunogenicity analyses, blood samples were drawn at identical study timepoints from six healthy adults, who did not receive any injections. The primary objectives of the study were safety and tolerability of the two dosage levels and reactogenicity after administration.Immunogenicity was assessed as a secondary endpoint by ELISA and neutralisation tests. T-cell immunity was evaluated by interferon-γ-linked enzyme-linked immune absorbent spot assay. All participants who were vaccinated at least once were included in the safety analysis. Immunogenicity was analysed in the participants who completed 6 months of follow-up. This trial is registered with ClinicalTrials.gov, NCT03615911, and EudraCT, 2014-003195-23

Findings From Dec 17, 2017, to June 5, 2018, 26 participants (14 in the low-dose group and 12 in the high-dose group) were enrolled and received the first dose of the vaccine according to their group allocation. Of these, 23 participants (12 in the low-dose group and 11 in the high-dose group) received a second dose of MVA-MERS-S according to their group allocation after a 28-day interval and completed follow-up. Homologous prime–boost immunisation with MVA-MERS-S revealed a benign safety profile with only transient mild-to-moderate reactogenicity. Participants had no severe or serious adverse events. 67 vaccine-related adverse events were reported in ten (71%) of 14 participants in the low-dose group, and 111 were reported in ten (83%) of 12 participants in the high-dose group. Solicited local reactions were the most common adverse events: pain was observed in 17 (65%; seven in the low-dose group vs ten in the high-dose group) participants, swelling in ten (38%; two vs eight) participants, and induration in ten (38%; one vs nine) participants. Headaches

observed in seven participants in the low-dose group vs nine in the high-dose group) and fatigue or malaise (ten vs seven participants) were the most common solicited systemic adverse events. All adverse events resolved swiftly (within 1–3 days) and without sequelae. Following booster immunisation, nine (75%) of 12 participants in the low-dose group and 11 (100%) participants in the high-dose group showed seroconversion using a MERS-CoV S1 ELISA at any timepoint during the study. Binding antibody titres correlated with MERS-CoV-specific neutralising antibodies (Spearman's correlation r=0·86 [95% CI 0·6960–0·9427], p=0·0001). MERS-CoV spike-specific T-cell responses were detected in ten (83%) of 12 immunised participants in the low-dose group and ten (91%) of 11 immunised participants in the high-dose group.

Interpretation Vaccination with MVA-MERS-S had a favourable safety profile without serious or severe adverse events. Homologous prime–boost immunisation induced humoral and cell-mediated responses against MERS-CoV. A dose– effect relationship was demonstrated for reactogenicity, but not for vaccine-induced immune responses. The data presented here support further clinical testing of MVA-MERS-S in larger cohorts to advance MERS vaccine development.

Funding German Center for Infection Research (DZIF).

STATEMENT:

We consider our work, 'Safety and immunogenicity of a modified vaccinia virus Ankara vector vaccine candidate for Middle East respiratory syndrome: an open-label, phase 1 trial' published on April 20th 2020 in The Lancet of Infectious Diseases to become the paper of the month (POM) because it describes the first-in-human safety and immunogenicity data of the MERS vaccine MVA-MERS-S. Until now, MVA-MERS-S had only been evaluated in dromedary camels where it showed protection against MERS-CoV. We here report the first safety and immunogenicity data with MERS vaccine candidate, which is the second MERS vaccine candidates tested in humans. We demonstrate the well tolerability of the vaccine in healthy volunteers. All vaccinees that received the higher dose generated MERS-S-specific antibodies, including neutralizing antibodies against MERS-CoV and T-cell responses. This is only the second vaccine candidate against MERS-Cov that was tested in humans and the first based on a vector technology, which may allow for a rapid response in developing vaccines against novel pathogens. The favourable profile of MVA-MERS-S could make a useful contribution to the development of future vaccine strategies against other coronavirus pathogens, such as the recently emerged SARS-CoV-2.

BACKGROUND:

This study was funded by the German Center for Infection Research (DZIF) and performed by the Lab group of Prof. Marylyn M. Addo, Head of the Division of Infectious Diseases of the I. Medical Clinic of the UKE. Dr. Till Koch, one of the first authors of the trial, works as a doctor in the I. Med and received a DZIF clinical leave stipend. Dr. Christine Dahlke, the other first author, is a senior postdoc scientist in Prof. Addo's UKE Lab group.