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Safety and immunogenicity of a mRNA rabies vaccine in healthy adults: an open-label, non-randomised, prospective, first-in-human phase 1 clinical trial

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Abstract

Background: Vaccines based on mRNA coding for antigens have been shown to be safe and immunogenic in preclinical models. We aimed to report results of the first-in-human proof-of-concept clinical trial in healthy adults of a prophylactic mRNA-based vaccine encoding rabies virus glycoprotein (CV7201).

Methods: We did an open-label, uncontrolled, prospective, phase 1 clinical trial at one centre in Munich, Germany. Healthy male and female volunteers (aged 18-40 years) with no history of rabies

vaccination were sequentially enrolled. They received three doses of CV7201 intradermally or intramuscularly by needle-syringe or one of three needle-free devices. Escalating doses were given to subsequent cohorts, and one cohort received a booster dose after 1 year. The primary endpoint was safety and tolerability. The secondary endpoint was to determine the lowest dose of CV7201 to elicit rabies virus neutralising titres equal to or greater than the WHO-specified protective antibody titre of 0·5 IU/mL. The study is continuing for long-term safety and immunogenicity follow-up. This trial is registered with ClinicalTrials.gov, number NCT02241135.

Findings: Between Oct 21, 2013, and Jan 11, 2016, we enrolled and vaccinated 101 participants with 306 doses of mRNA (80-640 μg) by needle-syringe (18 intradermally and 24 intramuscularly) or needle-free devices (46 intradermally and 13 intramuscularly). In the 7 days post vaccination, 60 (94%) of 64 intradermally vaccinated participants and 36 (97%) of 37 intramuscularly vaccinated participants reported solicited injection site reactions, and 50 (78%) of 64 intradermally vaccinated participants and 29 (78%) of 37 intramuscularly vaccinated participants reported solicited systemic adverse events, including ten grade 3 events. One unexpected, possibly related, serious adverse reaction that occurred 7 days after a 640 μg intramuscular dose resolved without sequelae. mRNA vaccination by needle-free intradermal or intramuscular device injection induced virus neutralising antibody titres of 0·5 IU/mL or more across dose levels and schedules in 32 (71%) of 45 participants given 80 μg or 160 μg CV7201 doses intradermally and six (46%) of 13 participants given 200 μg or 400 μg CV7201 doses intramuscularly. 1 year later, eight (57%) of 14 participants boosted with an 80 μg needle-free intradermal dose of CV7201 achieved titres of 0·5 IU/mL or more. Conversely, intradermal or intramuscular needle-syringe injection was ineffective, with only one participant (who received 320 μg intradermally) showing a detectable immune response.

Interpretation: This first-ever demonstration in human beings shows that a prophylactic mRNA-based candidate vaccine can induce boostable functional antibodies against a viral antigen when administered with a needle-free device, although not when injected by a needle-syringe. The vaccine was generally safe with a reasonable tolerability profile.

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Comment in

Is there a future for mRNAs as viral vaccines?

Warrell M.

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