Thermostable Subunit Vaccine Results in Protective Immunity in Rhesus Macaques in an Inhalational Ricin Model


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ABSTRACT

Ricin is a plant-derived toxin that, when inhaled in sufficient quantity, causes a rapidly progressive respiratory syndrome that can result in death. A vaccine derived from the A-chain moiety (RiVax®) has been developed by using conventional aluminum adjuvant, lyophilized in conjunction with glassifying excipients, and tested in a nonhuman primate (NHP) model of inhalational ricin toxicity. Rhesus macaques were either sham-vaccinated or vaccinated three times at one month apart with 100 micrograms of lyophilized vaccine reconstituted with Water for Injection. NHPs were exposed to an aerosolized ricin toxin (~3 x LD50) 45 days after the last vaccination. In the first of two cohorts of six NHPs each, all of the NHPs in the vaccinated group survived exposure (6/6), with no adverse signs of gross lung pathology. In the second cohort, 5/6 vaccinated NHPs survived; one NHP was euthanized on the 7th day post-exposure. Because a delayed death is atypical in this model, it is hypothesized that death was due to a secondary bacterial infection not related to ricin exposure; pathology is pending. All NHPs in both control groups (4/6) died within ~36 hours of exposure and developed severe lung damage, including characteristics hemorrhage and edema. All of the vaccinated NHPs developed ELISA-reactive antibodies (immunglobulin G (IgG) after two vaccinations and toxic neutralizing antibodies after the third vaccination. Previous studies with this lyophilization technology have demonstrated that the RiVax® vaccine is stable for at least 12 months at 40°C and the retained potency is associated, in part, with retention of the native configuration of the antigenic portion of the protein. Thus, this prototype vaccine overcomes cold-chain requirements. It has demonstrated safety and efficacy in a lethal aerosol NHP model of ricin toxicity. The results of this study indicate that RiVax® has great promise for protection against ricin exposure in humans and further clinical development of RiVax® is ongoing to establish its safety profile. This research was supported with funding from NIH/NIAID grant U01 AI08 2110.

RESULTS

Immune response to RiVaxTM-TR: Neutralizing Antibodies

Ricin Intoxication Associated with Changes in Body Temperature and Heart Rate

Neutrophilia Observed after Ricin In intoxication in both Sham and RiVaxTM-TR Vaccinated Animals

CONCLUSIONS

RiVax®-TR was 100% (11/11) efficacious in the NHP primate model of lethal aerosolized ricin toxin.

Animals were exposed to an aerosol of ricin 3-5 times the amount that is known to result in death of untreated animals.

RAC antibodies were significantly increased after 2 vaccinations while neutralizing antibodies were consistently elevated after 3 vaccinations.

Heart rate and temperature were significantly different in RiVax®-TR vaccinated animals by histopathology.

Neutrophilia occurred in both RiVax®-TR and Sham-vaccinated animals, indicating a robust innate immune response to ricin intoxication.