Effectiveness of a YF17D Subunit Vaccine with Adjuvant

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Abstract

An effective Yellow Fever vaccine has been in use for several decades. The live-attenuated 17D vaccine is very effective, induces long-term immunity and is protective. The vaccine, however, has some limitations, including the need for a cold chain, adverse events after infection of immunocompromised individuals and a reduced stockpile of vaccine due to recent outbreaks and renovation of vaccine production facilities. There is therefore a need for additional options for YFV vaccines and antivirals.

ViroVax has developed a subunit vaccine that is immunogenic and has shown protective efficacy. The vaccine is based on the effective 17D vaccine, but would not have the risks associated with a live-attenuated vaccine. The present study is designed to confirm this efficacy and to compare immunogenicity and protective efficacy with this vaccine and different adjuvants.

Materials and Methods

Animals: 95 female Syrian golden hamsters were used. Hamsters were assigned by weight to experimental groups and individually marked with ear tags.

Virus: Yellow fever virus (Jimenez hamster-adapted strain). A challenge dose of 200 CCID50 per hamster was administered via bilateral i.p. injections in a total volume of 0.2 mL.

Test agent: Alhydrogel, alhydroxyquim, and YF17D were provided by ViroVax for testing in the hamster model.

Infectious cell culture assay: Virus titer was quantified using an infectious cell culture assay where a specific volume of either tissue homogenate or serum was added to the first tube of a series of dilution tubes. Serial dilutions were made and added to Vero cells. Ten days later cytopathic effect (CPE) was used to identify the end-point of infection. Four replicates were used to calculate the 50% cell culture infectious doses (CCID50) per mL of plasma or gram of tissues.

Serum aminotransferase assays: Serum was collected via ocular sinus bleed on 6 days post-virus infection (dpi). ALT reagent was used, and the protocol was altered for use in 96-well plates. The plate was then read on a spectrophotometer, and aminotransferase concentrations were determined per manufacturer's instructions.

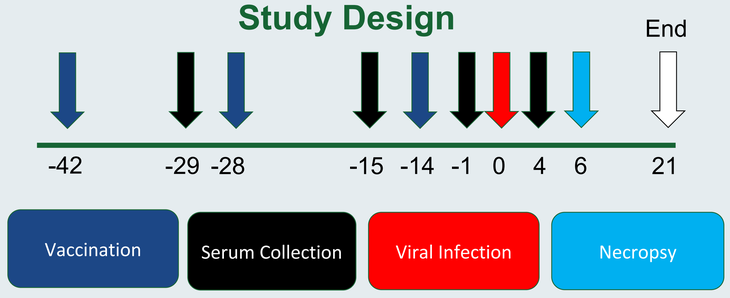
Rationale

- The existing Yellow Fever vaccine is effective but has certain risk factors associated with it as well as limitations in production and administration. These are common risk factors and limitations seen in many live attenuated vaccines.
- An effective subunit vaccine could avoid these risk factors.
- Previous studies of the subunit vaccine provided by ViroVax have shown efficacy and immunogenicity.
- If proven effective, a subunit YF17D vaccine could provide an alternative where the live attenuated vaccine is restricted.

Objectives

- Determine the effectiveness of the subunit vaccine with and without adjuvants.
- Effectiveness is measured through factors such as immunogenicity, survival of the test organism, and protection from symptoms.
- As stated above, if the vaccine meets all of these requirements, it could prove to be a practical alternative for the live attenuated vaccine is cases where it cannot be given (e.g. immunocompromised persons) or where it is not practical (e.g. where a cold chain cannot be sustained).

Study Design



Mortality

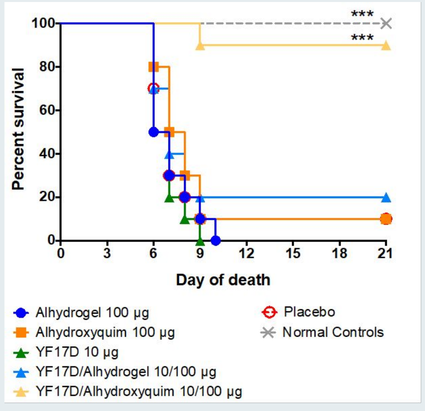


Figure 1. Mortality curves of Syrian golden hamsters after treatment with YF17D and/or alhydrogel or alhydroxyquim.

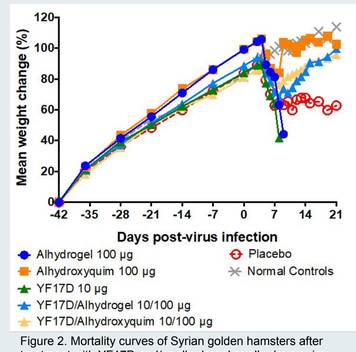


Figure 2. Mortality curves of Syrian golden hamsters after treatment with YF17D and/or alhydrogel or alhydroxyquim (***P<0.001 as compared to placebo treatment).

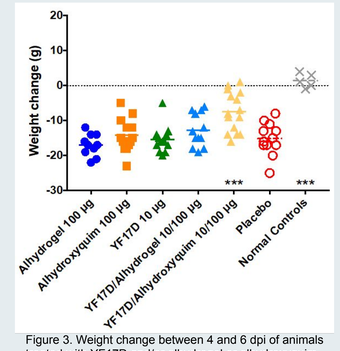


Figure 3. Weight change between 4 and 6 dpi of animals treated with YF17D and/or alhydrogel or alhydroxyquim (***P<0.001 as compared to placebo treatment).

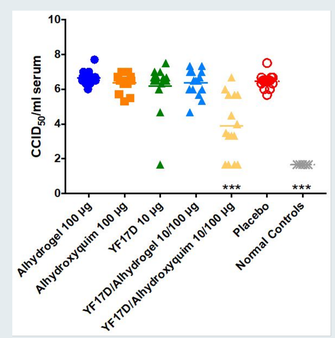


Figure 4. Viral titers from serum collected 4 dpi from animals treated with YF17D and/or alhydrogel or alhydroxyquim (***P<0.001 as compared to placebo treatment).

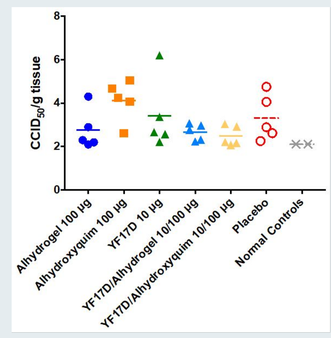


Figure 5. Viral titers from liver tissue collected 6 dpi from animals treated with YF17D and/or alhydrogel or alhydroxyquim.

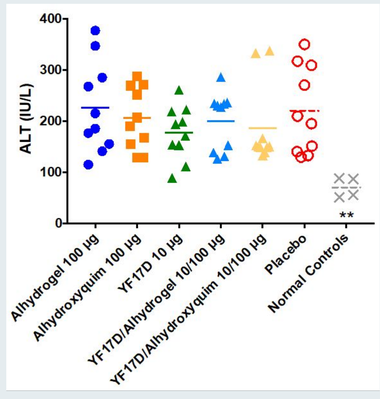


Figure 6. ALT levels of serum collected 6 dpi from animals treated YF17D and/or alhydrogel or alhydroxyquim (**P<0.01 as compared to placebo treatment). Samples from animals 344 and 384 were excluded due to hemolysis that could be considered a confounding variable.

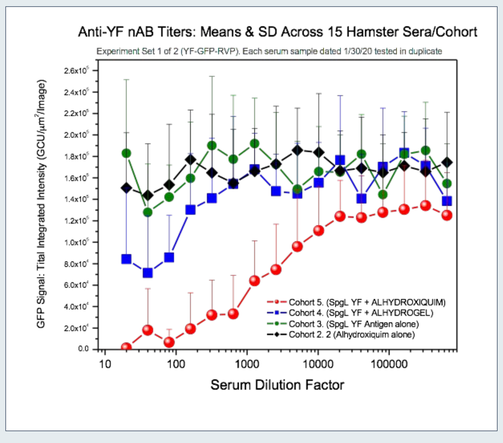


Figure 7. Neutralizing antibody curves of vaccinated group one day prior to virus challenge

Conclusion

Significantly improved survival, weight change and viremia, as well as a trend towards improved virus titer in the liver and ALT levels in the serum on 6 dpi, demonstrate efficacy of a domain III YFV 17D subunit vaccine administered with an alhydroxyquim adjuvant in a lethal hamster model of YF. The antigen alone or in combination with an alhydroxygel adjuvant were not effective, underscoring the importance of the alhydroxyquim adjuvant to the potency of this investigational vaccine.

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