EDITORIAL

An Inactivated Virus Candidate Vaccine to Prevent COVID-19

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The global struggle against coronavirus disease 2019 (COVID-19) is now in its eighth month since the pandemic virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first emerged. The severe economic, personal, and psychological adverse effects of shutdowns and social distancing make these effective preventive measures challenging to sustain long-term. In 1999, just before the launch of a new millennium, the Centers for Disease Control and Prevention listed vaccines as the most important public health achievement of the 20th century.[1] According to one estimate, more than 42 000 children's lives are saved annually as a result of the US programs of routine childhood immunizations.[2] Safe and effective COVID-19 vaccines could lead to a level of global immunity that stops the pandemic. This is the anti-COVID-19 intervention most public health leaders and many people long for the most.

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The RNA sequence of the SARS-CoV-2 genome was made public on January 10, 2020. Candidate vaccines emerged rapidly for human safety and immunogenicity studies. Interim reports of short-term follow-up after vaccination of tens or hundreds of study participants indicated that these candidate vaccines are safe and produce immune responses that might be protective.[3-8] Longer-term vaccine safety and the duration of vaccine-induced immune responses continue to be studied. The critical questions of vaccine efficacy and safety in thousands of participants will largely be answered in phase 3 vaccine efficacy trials, a few of which have recently begun.

The speed of COVID-19 vaccine development has led to questions about the safety of the vaccines. Are expected and required standards of scientific rigor being compromised in the race to effective vaccines? Will the vaccines be safe? Because vaccines are administered to healthy children and adults to keep them healthy, vaccine safety is of the utmost importance. The response to this legitimate concern should be strong and certain: there will be no compromises in the scientific assessment of vaccines in US clinical trials, even though the development processes are on accelerated timelines, as is appropriate in this global emergency. Vaccine developers and manufacturers, engaged US government agencies, and clinical trialists and laboratorians at academic institutions and clinical research organizations are achieving speed through intense effort; use of preexisting and rapid vaccine platforms (eg, RNA, nonreplicating viral vectors); and the performance of certain research steps and at-risk manufacturing in parallel rather than in series, in accordance with US Food and Drug Administration (FDA) guidance.[9] All standard safety assessments are being completed; to do less would be unethical.

The so-called genetic immunization candidate vaccines, including messenger RNA, DNA, and nonreplicating viral vectors such as recombinant adenovirus, were the first vaccine candidates to report interim results of early-phase clinical trials because these platforms are preexisting, flexible, rapid, and scalable. Therefore, genetic immunization approaches are particularly suited to a rapid pandemic response. While no genetic immunization vaccine has ever been licensed by the FDA for human use, these platforms hold great promise. Genetic immunization candidates can be seen as mimics of natural infection or of traditional live-attenuated vaccines, like the measles-mumps-rubella vaccine. These vaccines deliver instructions, encoded in nucleic acid sequences, that direct the body's cells to manufacture the vaccine protein in vivo. The safety of these vaccines will be of particular interest to scientists, regulators, and the public.

Protein immunogens are a different, and traditional, category of anticipated COVID-19 vaccines. Protein immunogens may be delivered as viral subunit proteins, viruslike particles, or as inactivated virus; are produced in a laboratory; and are often administered with an adjuvant to increase response magnitude and durability. The hepatitis A vaccine and the Salk inactivated polio vaccine are examples of licensed inactivated whole-virus vaccines.

In this issue of *JAMA*, Xia and colleagues[10] report results from an interim analysis of data for a SARS-CoV-2–inactivated virus vaccine plus adjuvant, the first protein immunogen COVID-19 vaccine candidate to be reported. The authors report preliminary findings from phase 1 and 2 randomized, active-controlled (aluminum hydroxide [alum]), double-blind, clinical trials of a β-propiolactone–inactivated SARS-CoV-2 vaccine adjuvanted in 0.5 mg of aluminum hydroxide. Healthy participants aged 18 to 59 years were enrolled and the trials were conducted in Henan Province, China. In phase 1, which included 96 healthy adults, 3 immunogen (inactivated virus) dose levels were studied (2.5, 5, and 10 μg, and an alum adjuvant–only dose; 24 participants in each group) and 3 vaccinations were administered on days 0, 28, and 56. For phase 2, which included 224 healthy adults, the middle dose (5 μg) was selected and administered twice at intervals shorter than in phase 1, either days 0 and 14 or days 0 and 21 (n = 84 in each group; plus 28 alum-only participants for each schedule).

Tolerability was assessed with a diary card, which participants completed for 7 days after each vaccination and recorded the presence, severity, and duration of solicited

local reactions (eg, injection site pain, redness, swelling) and solicited systemic reactions (eg, fever, headache, fatigue). Safety was assessed by analysis of blood chemistry and hematology at 4 days after each injection and by collection of unsolicited adverse events and serious adverse events occurring during the 28-day period after vaccinations. The primary immunogenicity end point was SARS-CoV-2 neutralization measured as a 50% plaque reduction neutralization test ($PRNT_{50}$) of serum samples collected 14 days after final vaccination.

This preliminary report indicates that the inactivated whole-virus vaccine candidate was tolerated, safe, and produced neutralizing antibodies at 14 days after booster vaccination. The primary safety outcome, 7-day postinjection adverse reactions, occurred in the phase 1 trial in 3 (12.5%), 5 (20.8%), 4 (16.7%), and 6 (25.0%) patients in the alum-only, low-dose, medium-dose, and high-dose groups, respectively, and in the phase 2 trial occurred in 5 (6.0%), 4 (14.3%), 16 (19.0%), and 5 (17.9%) patients in the days 0 and 14 vaccine, days 0 and 14 alum-only, days 0 and 21 vaccine, and days 0 and 21 alum-only groups, respectively. The most common adverse events were injection site pain, followed by fever, both of which were self-limited and mild. For the primary immunogenicity outcome, neutralizing antibody response at 14 days after the final booster vaccination, the geometric mean titers of neutralizing antibodies in the phase 1 trial in the low-, medium-, and high-dose groups were 316 (95% CI, 218-457), 206 (95% CI, 123-343), and 297 (95% CI, 208-424), respectively, and in the phase 2 trial were 121 (95% CI, 95-154) and 247 (95% CI, 176-345), respectively, in the days 0 and 14 and days 0 and 21 vaccine groups.

Acknowledged and acceptable limitations of the interim report of the ongoing phase 1/2 studies included the absence of data for persistence of antibody response, the absence of longer-term safety information, and the inability to assess vaccine protection against COVID-19. Additional follow-up in the ongoing phase 1/2 studies, and ultimately a phase 3 efficacy trial, would be required to address these important aspects.

The solicited local and systemic adverse reactions were not significantly different between the vaccine groups and the active control (alum) groups. This suggests that the adjuvant was responsible for the reactogenicity observed in the vaccine groups. The use of an active control agent that produces reactogenicity can be helpful for participant and investigator blinding to study group assignment, a design feature that was included in another phase 1/2 trial.[7]

Another limitation of this report is the absence of a comparison group to provide a benchmark for the magnitude of the reported serum neutralization titers in this $PRNT_{50}$ assay. Published studies of candidate COVID-19 vaccines have included the titers of serum neutralization of SARS-CoV-2 for convalescent patients who have recovered from COVID-19 illness.[5-7] Although a threshold titer of serum neutralization that is associated with protection against disease has not been identified, the titers of convalescent serum samples provide an imperfect positive control benchmark. Preferably, these control serum samples would be collected from recovered symptomatic patients at 4 to 6 weeks after onset of symptoms (to approximate the timing of early postvaccination serum samples) and be identified as outpatients vs hospitalized patients.

The authors also appropriately comment on the selection of β-propiolactone as the inactivating agent and of alum as the adjuvant. Alum is an adjuvant known to induce a T_H2-biased T-cell response. In earlier human trials of certain whole-virus inactivated vaccines (respiratory syncytial virus[11] and measles[12]), vaccine-associated enhanced respiratory disease was observed for formalin-inactivated, alum-adjuvanted vaccines, and a T_H2-like response was observed when natural infections occurred after vaccination.[13] Graham[13] has described these theoretical but important concerns, and the additional concern about antibody-dependent enhancement, for COVID-19 vaccine development and suggests approaches that may mitigate risk of human harm during development and testing of inactivated whole-virus vaccines.[13] In the Discussion section of their article, Xia et al[10] noted that antibody-dependent enhancement was not observed in vivo in a vaccination plus challenge model in nonhuman primates. In the supplemental information, the authors report immunophenotyping of circulating lymphocytes and serum cytokine levels after vaccination, but determination of the T_H1 vs T_H2 cytokines produced after vaccination by Th memory cells on restimulation by SARS-CoV-2 antigens in vitro is not reported and should be profiled.

In summary, this preliminary report by Xia et al[10] provides important interim safety, tolerability, and immune response results for a β-propiolactone–inactivated whole-virus vaccine against COVID-19. These interim data are of interest given the urgent global need for protective COVID-19 vaccines. With 7.8 billion individuals worldwide at risk for SARS-CoV-2 infection and COVID-19 morbidity and mortality, humanity needs as many safe and protective COVID-19 vaccines as possible.

ARTICLE INFORMATION

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