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Supplementary Materials for

Immunogenicity of clinically relevant SARS-CoV-2 vaccines in non-human primates and humans

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Supplementary Text

Since this article was re-submitted on 12/3/20, ten relevant papers and preprints appeared, along with several press releases and related media statements. Here, we briefly summarize the publications, with citations, and note other new developments.

The major events in this period were the FDA Emergency Use Authorizations of the Pfizer/BioNTech and Moderna mRNA vaccines https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19#new. Relevant press releases can be found on the Moderna and Pfizer/BioNTech websites. In the context of these approvals, the first evidence for vaccine prevention of asymptomatic infection in humans was presented https://www.fda.gov/media/144453/download. Other media announcements have referred to the efficacy of the Sinovac and Sinopharm (BIBP) inactivated vaccines in different countries e.g., the Middle East and Brazil), the status of the Gamaleya Institute's adenovirus vector vaccine trials, the commencement of the Novavax adjuvanted S-protein Phase 3 trial in the USA, and various updates on the AstraZeneca/Oxford adenovirus vector vaccine before and after its approval for use in the U.K.

Updates on mRNA vaccines

A Phase 3 trial showed that the Pfizer/BioNTech mRNA vaccine had an efficacy of 95% for preventing COVID-19. This finding underpinned the FDA's Emergency Use Authorization for this vaccine a few days later. In a secondary endpoint analysis, only one of ten cases of severe COVID-19 was in a vaccine recipient, the other nine in in the placebo group (74).

Data on the anti-RBD and NAb responses to the Moderna mRNA vaccine to day 119 were obtained in a subset of 34 volunteers in three different age-groups (18-55, 56-70 and over 70). The reduction in peak titers (day 43) with age was minimal, while titer declines between days 43 and 119 were also minor (~2-fold, but with considerable variation between individuals) (75).

Updates on adenovirus vector vaccines

In phase 1/2 trials of the AstraZeneca ChAdOx1 nCoV-19 adenovirus vaccine, the principal outcome was that two doses are required for optimal immunogenicity, which is the protocol eventually adopted for Phase 3. The phase 1/2 trials involve multiple small-scale dosing groups given either two full-doses or a full-dose and then a half-dose booster. It should be noted that this is the opposite order from the "dosing error" scenario that affected the Phase 3 trial (see below), where the low-dose was given first (76).

The outcome of the initial Phase 3 trials of the ChAdOx1 CoV-19 vaccine created considerable confusion and controversy about the level of efficacy achieved. Different sub-trials in the U.K. and Brazil contributed to the data. A complication was an apparent dose-calculation error that caused the first dose of the two-dose regimen to be ~2-fold lower than was intended. The reported efficacy for this sub-group was 90%, whereas efficacy was considerably less, at 60-65%, when two standard doses were given. Data from additional and/or projected Phase 3 trials may resolve any uncertainties (77).

A new adenovirus vaccine was based on the Ad5-serotype that was modified to reduce the immunogenicity of the virus vector components. In a rhesus macaque study, combinations of sub-cutaneous and oral delivery (3 doses given in total over 42 days) were evaluated for antibody and T-cell induction. After intranasal virus challenge, the vaccinated animals had lower and more rapidly cleared VLs in the nose and lungs. A Phase 1 human trial involving sub-cutaneous delivery has been completed, while oral delivery will be tested in a new trial (78).

Updates on inactivated virus vaccines

Two reports described some basic *in vitro* properties of the Sinopharm/WIBP inactivated virus and its immunogenicity in several animal species, including cynomolgus and rhesus macaques (79, 80). This vaccine is in late stage clinical trials.

The BBV152 inactivated virus vaccine, from the Indian Council of Medical Research and Bharat Biotech in India, is based on the SARS-CoV-2 NIV-2020-770 strain, which contains the D614G mutation. In both the Phase 1 and Phase 2 trials, three different formulations were studied in a two-dose regimen (days 0 and 14): A 6 μg dose in Algel (Alum) vs. 3 μg and 6 μg doses in Algel-IMDG, which is Alum containing a small-molecule TLR7/8 activator. After the Phase 2 trial, the 6 μg dose in Algel-IMDG was selected for the ongoing Phase 3 trial (81, 82)

Update on protein-based vaccine

The ZF2001 vaccine candidate is produced by a consortium centered on the Chinese Academy of Medical Sciences in Beijing and is a CHO cell-expressed, Alum-adjuvanted RBD-dimer. The clinical trials evaluated three doses of either 25 or 50 μg that were given on days 0, 30 and 60. The antibody data showed that the third dose was necessary to induce strong responses. This vaccine is now in Phase 3 trials (83).