Immunogenicity of SCB-2019 COVID-19 Vaccine Compared to Four Approved Vaccines

Donna Ambrosino

Htay Htay Han

Clover Biopharmaceuticals

Branda Hu

Clover Biopharmaceuticals

Joshua Liang

Clover Biopharmaceuticals

Ralf Clemens

Global Research in Infectious Diseases

Marina Johnson

Great Ormond Street Institute of Child Health

George Siber

David Goldblatt (✉ d.goldblatt@ucl.ac.uk)

Great Ormond Street Children's Hospital NHS Foundation Trust

Research Article

Keywords: COVID-19 Vaccines, SCB-2019, Immunogenicity, Antibody

Posted Date: September 14th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-902086/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

A significant correlation has been shown between the binding antibody responses against original SARS-CoV-2-S-protein all performed in one laboratory and vaccine efficacy of four approved COVID-19 vaccines. We therefore assessed the immune response against original SARS-CoV-2 elicited by the adjuvanted S-Trimer vaccine, SCB-2019 + CpG/alum, in the same assay and laboratory. When compared with four approved vaccines immune responses to SCB-2019 predicted 81% – 94% efficacy against the original strain and 75–94% against the Alpha variant (B.1.1.7). Immunogenicity comparisons to original strain and variants of concern (VOC) should be considered as a basis for authorization of vaccines because efficacy studies now have predominantly VOC cases.

Background

Intensive research efforts to develop novel SARS-CoV-2 virus vaccines to protect against the global COVID-19 pandemic have resulted in many different vaccines but with only a few currently authorized for use. Most are based on the Spike (S) protein sequence of the original wild-type SARS-CoV-2 virus isolated in Wuhan, China or inactivated whole virus [1, 2]. Immunological results from the various vaccine candidates assessed in multiple studies by different laboratories use their own unique antibody binding or neutralization assays. Differences in these assays makes it difficult to compare and interpret the relative potencies of the various S-protein vaccines. The use of different vaccine platforms theoretically further complicates comparison among vaccines. However, in spite of these differences, a strong correlation of antibody responses and efficacy have been reported even when using the imperfect calibration with antibody responses of convalescent patients measured in the same assay (3,4). Recently Goldblatt and colleagues have overcome these limitations by comparing binding antibody responses in subjects vaccinated with one or two doses of approved vaccines measured in a single laboratory using an ELISA IgG assay against S-protein calibrated with the WHO international standard and reported as binding antibody units (BAU)/ml. A highly statistically significant correlation was found between their calibrated geometric mean antibody concentrations and the clinical efficacies of those vaccines obtained from large-scale clinical trials [5].

Clover Biopharmaceuticals have applied their innovative S-Trimer technology to develop a subunit vaccine candidate, SCB-2019 + CpG/alum, a stabilized pre-fusion form of the SARS-CoV-2 S-protein adjuvanted with the toll-like receptor (TLR) agonist CpG-1018 and alum. In a phase 1 study SCB-2019 + CpG/alum was shown to be well tolerated and immunogenic in adults from 18 to 75 years of age [6]. Subsequent follow-up has shown persistence of the immune responses to 6 months and provided an initial demonstration of neutralizing activity against several SARS-CoV-2 Variants of Concern [7].

A major phase 2/3 trial (SPECTRA) is ongoing to assess the efficacy of SCB-2019 + CpG/alum in preventing COVID-19 illness (EudraCT number, 2020-004272-17). Due to the current epidemiology in the countries where the vaccine trial is being conducted, the vast majority of cases will be variants of concern (VOC), precluding direct estimation of efficacy to the original strain. We therefore compared vaccine

induced immunological responses of subjects in that study to responses to four COVID-19 vaccines currently in clinical use, to provide a predicted vaccine efficacy against the original virus and the Alpha (B.1.1.7) variant.

Methods

In Clover's SPECTRA phase 2/3 efficacy trial approximately 30,000 volunteers aged 18–75 years have been recruited in the Philippines, Colombia, Belgium, Brazil, and South Africa and randomized to receive two immunizations three weeks apart with either SCB-2019 + CpG/alum or placebo (0.9% saline). The trial is being performed in concordance with ICH and GCP guidelines and with the signed informed consent of all volunteer participants. The study protocol and amendments were approved by IRB and registered (EudraCT number, 2020-004272-17). A subset of phase 2 participants was evaluated for B- and T-cell immune responses at two weeks after the second vaccination (Day 36), and sera were collected from all participants for use in estimating correlates of protection. Sera at baseline were also assessed for prior exposure to SARS-CoV-2 with the Elecsys[®] SARS-CoV-2 S ELISA kit (Roche, Basel, Switzerland). For the additional analysis reported here an unblinded statistician randomly selected Day 36 sera from participants who were seronegative at baseline, 100 from vaccinees and 20 from placebo recipients, stratified across two age ranges of 18–60 yrs and ≥ 60 yrs. The final selection of 120 sera included participants from the Philippines ($n = 50$), Colombia (51), Belgium (14) and South Africa (5). The samples for vaccine recipients included 90 from those aged from 18 to 59 years (32 from < 30 yrs, 35 from 30–39 yrs, 23 from 40–59 yrs), and 10 from ≥ 60 yrs. The selected sera were tested in the Goldblatt laboratory in a blinded manner using a multiplex assay for IgG binding the S-protein and spike receptor binding domain (RBD) of the original Wuhan strain of SARS-CoV-2 and of the Alpha variant (B.1.1.7) as previously described [5]. Results were calibrated with the WHO international standard serum and expressed in binding antigen units (BAU) per mL. The final data from the vaccinees are presented as BAU concentrations for individual sera and as geometric mean concentrations (GMC) for each age group; data for placebo recipients which were all negative are not included in this report to be consistent with the reported data for the four approved vaccines. The demographic characteristics of the naïve vaccine cohorts for the four approved vaccines are detailed previously (5). The antibody geometric mean concentrations were compared by rank sum paired tests corrected by Dunn's multiple test.

Results & Discussion

Individual results for IgG binding to S-protein from the original strain and Alpha variant expressed as BAU/mL for all five cohorts are shown in Fig. 1. The GMC (95% CI) of Clover vaccine recipients following two doses for original spike was 1010 BAU/ml [752–1355] as compared to GMC following two doses for mRNA-1273 (5530 BAU/mL [4007–7633]), BNT162b2 (2653 BAU/mL [2071–3399]), ChAdOx1 nCoV-19 (196 BAU/mL [140–273] and after one dose of Ad.26COV2.s (61 BAU/ml [37–101]). The Clover vaccine recipients GMC was significantly higher to both original and Alpha variant than ChAdOx1nCoV-19 vaccine cohort ($p < 0.0001$) and Ad.26COVV2.s vaccine cohort ($P < 0.0001$) and significantly lower when

compared to Pfizer and Moderna ($P < 0.0001$). Responses to the RBD for original and Alpha variant showed similar results with Clover GMC significantly higher for ChadOx1nCoV-19 ($p = 0.0009$ for original and $p = 0.0013$ for alpha) and Ad.26COVV2.s cohorts ($p < 0.0001$ for both). Of note, the younger Clover adults generally displayed higher response against S-protein and RBD for original prototype and Alpha variant compared to the older adults (Table 1). However, the older adults had a GMC that was still higher than GMC for both the ChAdOx1nCoV-19 and Ad.26COV2.S entire vaccine cohorts which each contained older adults (5).

Table 1

Age specific Geometric Mean Concentrations (GMC) of IgG Binding Antibody Units (BAU/mL) assessed by ELISA against S-protein and RBD of the original prototype SARS-CoV-2 and of the Alpha variant (B.1.1.7) in participants vaccinated with SCB-2019

Virus and Antigen					
		Original prototype		Alpha variant	
Age		S-protein	RBD	S-protein	RBD
18–60 years	n	90	90	90	90
	GMC (BAU/mL)	1097	1217	700	1259
	[95% CI]	[802–1502]	[889–1666]	[511–961]	[933–1699]
≥ 60 years	n	10	10	10	10
	GMC (BAU/mL)	477	430	345	481
	[95% CI]	[215–1057]	[135–1365]	[153–779]	[150–1542]

Major issue for licensure of new COVID-19 vaccines is twofold: Firstly, the conduct of controlled field efficacy trials is hampered by the fact that placebo control is at this stage deemed unethical by most ethical review boards whilst the comparison of a new candidate to an approved vaccine is operationally problematic because of the limited access of approved Covid-19 vaccines for clinical trials. Secondly, assessing clinical efficacy against an evolving background of disease incidence due to new variants replacing the original prototype Wuhan-Hu-1 virus. At the time of this report, COVID-19 in most of the world is caused predominantly by VOC including the Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), Gamma (P.1), Mu (B.1.621) and other variants. Many of the variants have reduced sensitivity to antibody compared to original and alpha and currently approved vaccines are showing lower efficacy/effectiveness against VOCs than original virus (8–10). As it is no longer feasible to evaluate or compare clinical efficacy of new vaccines to approved vaccines against the original strain, it has become critically important to compare new vaccines to the approved vaccines based on immunogenicity to the original strain and VOC rather than clinical efficacy. As noted, our group previously reported that binding antibody was correlated to efficacy and also highly correlated with neutralization antibody. We and others also suggest that binding antibody comparisons may be superior choice due technical simplicity, lower

variability, easier standardization and ability to assess neutralizing as well non-neutralizing antibody activities. (4,11).

For the four approved vaccines compared in this report, efficacies were 94.1% (95% CI: 89.3–96.8) [12], 94.6% (89.9–97.3) [13] and 80.7% (66.5–88.9) [14] against symptomatic disease of original virus after two doses for mRNA-1273, BNT162b2 and ChAdOx1 nCoV-19, respectively, and 72.0% (58.2–81.7) after one dose of Ad26.COV2.S [15]. The binding antibody response for SCB-2019 + CpG/alum to the original virus predicts an efficacy rate in a range of 81–94%. Furthermore, GMCs of binding antibody to Alpha variant compared favorably to the approved vaccine responses, and thus acceptable efficacy against Alpha variant is predicted within the on-going trial by Clover. However other VOC with lower levels of cross reactivity with the original strains are expected to be predominant in this trial and thus overall efficacy is predicted to be lower than for the original strain.

We therefore suggest that immunogenicity comparisons need to be considered for authorization of new vaccines because the predominance of VOC in ongoing trials will make current efficacy guidelines based on the original strain challenging or impossible to achieve. We further propose an approach to conduct such comparisons that would require co-operation among multiple stakeholders: namely to assemble adequately sized banks of post immunization sera from licensed vaccines to support direct comparisons with responses to new vaccines for non-inferiority. The comparisons could be done in an independent blinded manner against the original strain and VOCs. We suggest that binding antibody may be best suited for these comparisons provided that a strong correlations between binding and neutralization for original strain and VOCs have been established. Utilizing an established serum bank would avoid the requirement of securing comparator vaccines by all developers in many different locations and avoid lengthy head-to-head non-inferiority trials which would delay timely availability of much needed safe and effective additional vaccines.

Conclusions

The adjuvanted SCB-2019 COVID-19 vaccine candidate demonstrates comparable or superior immunogenicity for both original and Alpha variant to four approved vaccines. The on-going placebo controlled trial will evaluate efficacy against many VOC for which approved vaccines do not have comparable clinical data and include variants with significantly reduced sensitivity to antibody. Thus, comparable immunogenicity data to original virus and variants between new vaccines and approved vaccines should be considered for authorization when conducted in a robust independent manner utilizing standardized appropriate assays preferably within the same laboratory.

Declarations

Authors Contributions

All authors contributed to the design of the study, writing of the study and revision of the manuscript. Additionally, DG, was responsible for sample collection for the four approved vaccine cohorts, HH, BH, JL were responsible for design and collection of samples for SCB-2019 sera, and MJ was responsible for laboratory evaluation of samples.

Competing Interests statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Siber reports personal

fees and other from Clover Biopharmaceuticals, personal fees from AdVaccine, other from Vaxxinity personal fees from CanSino, personal fees from CureVac, personal fees from Valneva, personal fees from Vaxart, personal fees and other from Affinivax, outside the submitted work; Dr. Ambrosino reports personal fees from Vaxxinity, personal fees and other from Clover Biopharmaceuticals, outside the submitted work. RC reports personal fees from Clover Biopharmaceuticals, and outside the submitted work personal fees from CureVac, Valneva and Icosavax.

References

1. Huang Y, Yang C, Xu X-F, Xu W, Liu S-W. Structural and functional properties of SARS-CoV-2 spike protein: potential antiviral drug development for COVID-19. *Acta Pharmacol Sin* 2020; 41: 1141–9.
2. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. *Nature* 2020; 579(7798): 265–9.
3. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021; 27,1205–11.
4. Earle KA, Ambrosino DA, Fiore-Gartland A, et al. Evidence for antibody as a protective correlate for COVID-19 vaccines. *Vaccine* 39,4423-4428 (2021).
5. Goldblatt D, Fiore-Gartland A, Johnson M, et al. A population-based threshold of protection for COVID-19 vaccines. 31 Aug, 2021 PREPRINT (version 1) available at Research Square. DOI: <https://doi.org/10.21203/rs.3.rs-832531/v1>
6. Richmond P, Hatchuel L, Dong M, et al. Safety and immunogenicity of S-Trimer (SCB-2019), a protein subunit vaccine candidate for COVID-19 in healthy adults: a phase 1, randomised, double-blind, placebo-controlled trial. *Lancet* 2021; 397(10275): 682–94.
7. Richmond P, Hatchuel L, Pacciarini F, et al. Persistence of the immune responses and cross-neutralizing activity with Variants of Concern following two doses of adjuvanted SCB-2019 COVID-19 vaccine. *J Infect Dis* Accepted September 4th, 2021. Available online at: <https://doi.org/10.1093/infdis/jiab447>
8. Uriu, K, Kimura I, Shirakawa K, et al. Ineffective neutralization of the SARS-CoV-2 Mu variant by convalescent and vaccine sera. September 7, 2021. PREPRINT available at bioRxiv. DOI: <https://doi.org/10.1101/2021.09.06.459005>

9. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. *N Engl J Med* 2021; 385:585–94.
10. Sheikh A, McMenamin J, Taylor B, et al. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet* 2021; 397, 2461-2462.
11. Carreño J, Alshammary H, Singh G., et al. Reduced neutralizing activity of post-SARS-CoV-2 vaccination serum against variants B.1.617.2, B.1.351, B.1.1.7+E484K and a sub-variant of C.37. *medRxiv*, DOI: <https://doi.org/10.1101/2021.07.21.21260961>
12. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021; 384: 403–16.
13. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2021; 383: 2603–15.
14. Voysey M, Costa Clemens SA, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet* 2021; 397, 881–91.
15. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. *New Engl J Med* 2021; 384: 2187–201.

Figures

Figure 1

IgG binding antibody to S-protein from the original type SARS-CoV-2 and the Alpha variant of 100 adults vaccinated with SCB-2019 compared to the antibody responses of cohorts immunized with each of four approved vaccines. The geometric mean concentrations (95% CI) are shown above each group and responses to SCB-2019 were significantly higher than both ChadOx1nCoV-19 and Ad26.COV2.s vaccine groups ($p<0.0001$) and significantly lower than mRNA-1273 ($p<0.0001$) and BNT-162b ($p=0.0009$) vaccine groups for both original and alpha variant utilizing rank sum unpaired tests adjusted by Dunn's multiple test.