Review of: "Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant"

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Despite the unprecedented development of vaccines against the COVID-19 pandemic, major concerns have been raised in the wake of the appearance of novel more transmissible and pathogenic SARS-CoV-2 variants, and particularly whether the existing vaccines can provide protection. In this context, the timely clinical trial for the simian adenovirus-based ChAdOx1 nCoV-19 vaccine against the South African B.1.351 variant [1] is worth a deeper analysis and comparison to other COVID-19 vaccines evaluated for efficacy against SARS-CoV-2 variants. In the multi-center, double-blind, randomized, controlled, phase II clinical trial, conducted in South Africa in 2026 HIV-negative adults from the age group 18-65 years, received either two doses of 5 x 10^{10} ChAdOx1 nCoV-19 particles or placebo 21 to 35 days apart. The conclusions of the study are rather disappointing indicating that the ChAdOx1 nCoV-19 vaccine did not show protection against mild-to-moderate COVID-19 caused by the B.1.351 variant.

Initially, 3022 individuals were screened resulting in 1010 participants receiving the vaccine and 1011 individuals were subjected to placebo. The median age of the patients was 30 years and 56.5% were male. According to the publication, 70.5% were Black Africans, 12.8% White, 14.9% of mixed race and the rest 1.8% of other races. Among the participants, 19% were obese, 42% smokers, 2.8% had underlying hypertension and 3.1% had chronic respiratory conditions.

Evaluation of administration safety demonstrated that local and systemic reactogenicity was similar among individuals receiving vaccine and placebo. Only a single serious adverse event was registered for the ChAdOx1 nCoV-19 vaccine after the first dose, where the vaccinee developed a fever response of 40°C, which subsided within 24 hours. No reactogenicity was detected after the second dose.

Strong humoral immune responses were observed after the first immunization with ChAdOx1 nCoV-19 with a further enhancement seen after the second vaccination. Moreover, the neutralizing activity against the B.1.351 variant was evaluated with pseudovirus and live-virus assays [2,3] in 25 individuals, who were SARS-CoV-2 seronegative at enrolment but showed neutralizing antibody activity against SARS-CoV-2 D614G 14 days after the second vaccination. Six of the 25 individuals belonged to the placebo group and had most likely been infected with the original SARS-CoV-2 strain prior to the spread of the B.1.351 variant in South Africa. Moreover, PCR testing demonstrated that 6 vaccine recipients were infected with SARS-CoV-2 14 days after the second vaccination. Neutralization activity measurements using a receptor binding domain (RBD) triple mutant (K417N, E484K, and N501Y) pseudovirus showed no activity in 6 of 13 vaccine

recipients with no previous SARS-CoV-2 infection. Moreover, 11 or the 13 vaccinees showed no neutralization activity against the B.1.351 pseudovirus.

The overall neutralization activity was lower in live-virus assays compared to pseudovirus assays. Among the 13 vaccinees with no previous SARS-CoV-2 infection, one individual showed no neutralization activity neither against the B.1.1.7 nor the B.1.351 variants. Although 7 of 12 vaccinees showed neutralization activity against the B.1.1.1 variant, no activity was detected against the B.1.351 variant. In the 5 remaining individuals the neutralization activity was 4.1 to 31.5-fold lower. The previously mentioned 6 SARS-CoV-2 infected individuals from the placebo group showed detectable neutralization of the B1.1.7 variant but not the B.1.351 variant. Due to the importance of T-cell based protection of COVID-19, 17 individuals vaccinated with the ChAdOx1 nCoV-19 vaccine were evaluated, which showed expansion of CD4+ and CD8+ lymphocytes to specific epitopes of the SARS-CoV-2 S protein. Interestingly, the B.1.351 variant did not affect 75 S-specific antigens of the total of 87 identified by sequencing. Moreover, the B.1.351 variant hosts the D215G mutation, which is in the region of prevalent T-cell antigen responses.

All 42 cases of COVID-19 in the study were graded as mild-to-moderate and no patient required hospitalization. Sequence data from 41 of the 42 patients confirmed that 39 (95.1%) of individuals had been infected by the B.1.351 variant and the two remaining individuals by the B.1.1.1 and B1.144 lineages [4]. The overall vaccine efficacy for COVID-19 after the first dose was estimated to be 33.5%. Moreover, a post hoc analysis at more than 14 days after the first injection indicated that the overall attack rate of mild-to-moderate COVID-19 manifestation was 1.3% for the placebo group and 0.3% for vaccine recipients [5].

In summary, the clinical trial on ChAdOx1 nCoV-19 against the SARS-CoV-2 B.1.351 variant indicated that vaccination showed no efficacy in preventing mild-to-moderate COVID-19. However, no severe cases of COVID-19 occurred, which would require hospitalization. In contrast, before the South African B.1.351 variant appeared the ChAdOx1 generated 75% efficacy in preventing mild-to-moderate COVID-19 even after a single dose. Therefore, it was estimated that the vaccine would provide at least 60% efficacy in prevention of COVID-19 of any severity even in the presence of the B.1.351 variant. Moreover, because the demographic and clinical profiles of enrolled participants excluded severe cases of COVID-19 cases the findings in relation to the capacity of vaccine protection against severe COVID-19 disease are inconclusive. Reduced or abrogated ChAdOx1 nCoV-19-induced antibody neutralization against the B.1.351 variant was confirmed by pseudovirus and live-virus neutralization assays. In contrast, pseudovirus neutralization responses to the original SARS-CoV-2 strain showed similar results for ChAdOx1 nCoV-19 vaccinations as in other studies conducted in the UK and Brazil [6].

A question of significant interest is whether enhanced immune responses can be achieved by extending the time between the first and second immunization [6,7], which could also improve the neutralization activity against the B.1.351 variant. Another issue relates to the efficacy of other COVID-19 vaccines against the B.1.351 variant in comparison to the ChAdOx1 nCoV-19 vaccine. In this context. The RNA-based COVID-19 vaccines BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) elicit modest levels of neutralizing antibodies after the first immunization with a substantial increase in neutralizing activity after the second vaccination [8,9]. Generally, the neutralization activity has been superior for these RNA-based vaccines that seen for ChAdOx1 nCoV-19 and the heterologous adenovirus-based Sputnik V vaccine applying an adenovirus serotype 26 vector expressing the SARS-CoV-2 S protein for prime immunization and serotype 5

vector expressing the SARS-CoV-2 S protein for the boost immunization [10]. Related to the B.1.351 variant, both the BNT162b2 and mRNA-1273 vaccines have demonstrated reduced neutralization activity. In pseudovirus assays the activity against B.1.351 was 6,5-fold and 8.6-fold lower for BNT162b2 [11] and mRNA-1273 [12], respectively, compared to the SARS-CoV-2 D614G mutant. In contrast, there was no reduction in neutralization activity against the B.1.1.7 variant [13]. Moreover, the NVX-CoV2373 nanoparticle encapsulated protein subunit COVID-19 vaccine has showed 95.6% effectivity against the original SARS-CoV-2 and although reduced substantial protection of 85.6% against the B.1.1.7 variant and 60% against the B.1.351 variant [14].

A very recent study, taken into account the presence of the B.1.351 variant, was conducted in several countries including South Africa for the single-dose adenovirus serotype 26 SARS-CoV.2 S vaccine (Ad26.COV2.S) [15]. The results showed 57% efficacy against mild-to-moderate COVID-19 and 89% efficacy against severe disease. However, only COVID-19 cases confirmed by PCR in patients with at least 3 symptoms were accepted for end-point acceptance, which likely excluded cases of mild COVID-19. Furthermore, the study did not include neutralization activity assays against the B.1.351 variant.

The importance of neutralizing antibody responses has been confirmed by the correlation between antibody response and vaccine efficacy. However, T-cell responses have also been postulated to paly an important role in protection against COVID-19 if antibody responses are suboptimal as has been demonstrated in rhesus macaques [16]. This was also confirmed by intact recognition of the B.1.351 variant in the majority of antigens and epitopes was detected in SARS-CoV-2 S-specific T-cells expanded after vaccination with ChAdOx1 nCoV-19 [1].

Finally, as RNA viruses such as SARS-CoV-2 have strong tendency to generate novel mutants to escape immune recognition it is therefore of utmost importance that vaccine efficacy is evaluated against any new variants. Although significant efforts are in progress to develop second-generation COVID-19 vaccines, which target current variants such as B.1.351 and B.1.1.7, the demand for rapid global mass vaccinations indicate that we have to rely on current available COVID-19 vaccines. Therefore, it is important to confirm that these vaccines show high efficacy and are safe to use. In this context, the study on efficacy of ChAdOx1 nCoV-19 against the South African B.1.351 variant is of great importance [1].

Another very recent issue with adenovirus-based COVID-19 vaccines relates to the finding that in some rare cases vaccination have caused thrombotic thrombocytopenia [17]. However, the low rate of incidences should not discourage the continuation of mass vaccinations but should instead encourage investment in more research to better understand the cause of thrombocytopenia after adenovirus-based vaccinations and to find a solution for its prevention.

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