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Perspective

The conundrum of two-dose interval of ChAdOx1 nCOV-19 corona virus vaccine: Way ahead

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has not only surpassed all projections but even after one year of its origin, it continues to create havoc across the globe. As per the current understanding, the clinical presentation of COVID-19 may range from asymptomatic to a fatal outcome; yet majority of the patients (almost 80%) have been seen to have a mild disease.[1] The causative agent of COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), through the receptor-binding domain present on its spike (S) protein, gains entry into a human cell by binding the angiotensin-converting enzyme 2 receptors.[2] This signifies that antibodies neutralizing the S-protein may be effective in providing protection against COVID-19. The presence of a virus neutralizing antibody is the main determinant of protection against COIVD-19.[3] Therefore, the development of population immunity either through vaccination or by a natural infection is essential for combating the COVID-19 pandemic. However, the exact mechanism for the development of lasting protective immunity is yet to be completely understood.[4]

Although the duration of detectable antibodies is variable in different studies, most of the evidence indicate that these neutralizing antibodies do not prevail at a detectable level after 3–4 months of initial illness. One study reported rapid waning of antibodies so much so that a third of patients lost neutralizing antibodies by around 1–2 months after the onset of illness.[5] However, some studies observed that seroconverted patients (with both mild and severe symptoms) retain detectable IgG levels even after 75 days post initial symptoms.[6]

The much-awaited ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) (marketed as COVISHIELD) was approved for emergency or conditional use in India on 01 January 2021 by the Drug Controller General of India. India from 16th January 2021 started administering COVISHIELD initially at an interval of 4 weeks,[7] which was subsequently increased to 6–8 weeks, and recently the policy has been again revised to increase the interval between two doses to 12–16 weeks. The present paper aims to highlight the available literature concerning the immune response and efficacy of ChAdOx1 nCoV-19 (AZD1222) and recommends a way ahead regarding optimum interval between two doses of COVID vaccine.

Science behind ChAdOx1 nCoV-19 (AZD1222)

The ChAdOx1 nCoV-19 vaccine consists of the SARS-CoV-2 structural surface antigen (spike protein) gene contained in a

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non-replicating chimpanzee adenoviral vector ChAdOx1. In the rhesus macaque challenge model, the "neutralizing antibody (NAb)" developed post-vaccination with spike antigen has been found to provide protection against SARS-CoV-2.[8,9] The Nab antibodies have also been detected in convalescent COVID-19 patients and the degree of the antibody response is said to be directly related to antigen load, that is, patients with severe disease are likely to have enhanced response as compared to patients with mild disease.[10–13] The NAb besides directly neutralizing the virus has many diverse functions such as "antibody-dependent neutrophil phagocytosis, antibody-dependent natural killer (NK) cell degranulation, antibody-dependent complement deposition, and antibody-dependent cellular phagocytosis" which ultimately determines disease progression and protection against reinfection.[13,14] In addition, the role T cell against SARS-CoV-2 has also been ascribed for protection and early recovery from COVID-19.[15]

Immunological response to ChAdOx1 nCoV-19 (AZD1222) vaccine

The immunological response to ChAdOx1 nCoV-19 (AZD1222) vaccine can be broadly summarized as anti-spike antibody class and subclass, antibody-dependent monocyte/neutrophil phagocytosis (ADMP/ADNP) and cellular response. The salient features of each type of immune response are as follows:[16]

(a) **Types and subtypes of anti-spike antibody.** Studies have indicated that vaccination with ChAdOx1 nCoV-19 resulted in an increase in anti-spike IgM and IgA titers with the peak occurring at 28 days post-vaccination. Similarly, subclasses of anti-spike IgG i.e IgG1 and IgG3 were detectable 28 days after the 1st dose of vaccination and continued to persist at the same levels till 56 days. In the case of a booster dose, IgG1 levels increased when the booster dose was given at 56 days interval but failed to show response when the booster was given at 28 days interval. IgG3 levels were found to increase in both 28 and 56 days booster dose regimens.

(b) **Functional aspects of anti-spike antibody.** Research studies investigating the anti-spike antibody ability to induce antibody-dependent monocyte phagocytosis (ADMP) and antibody-dependent neutrophil phagocytosis (ADNP) have found induction of both the functions post 1st dose vaccination and a significant increase in response after the second dose. However, the ADMP and ADNP response were much higher when the second dose was given after an interval of 56 days as compared to 28 days. Similarly, single-dose vaccination with ChAdOx1 nCoV-19 vaccine induced antibody-dependent complement deposition and higher median fluorescence intensity, when the booster was administered after 56 days interval.

(c) **Anti-spike antibody-dependent natural killer cell activation (ADNKA).** ChAdOx1 nCoV-19 vaccine has been reported to induce "anti-spike antibody-dependent NK cell activation (ADNKA)" by triggering expression of CD107a. However, low levels of ADKNA were induced by a single dose of ChAdOx1 nCoV-19 and need to be boosted by a second dose. ADKNA levels measured after 14 days of the second dose were found to be much lower when the second dose was given at an interval of 28 days (***median: 3.96, IQR: 3.44–5.36***) as compared to an interval of 56 days (median: 5.29, IQR: 3.61–6.13).[16]

(d) **Response at the cellular level.** After 14 days of first dose of vaccination, researchers have demonstrated induction and peaking of antigen-specific T cell responses. But there was no difference in spike-specific T cells responses when the booster dose was given at two different intervals, that is, 28 days and 56 days from the initial vaccination.

Efficacy and dose interval of the ChAdOx1 nCoV-19 (AZD1222) vaccine

The vaccine manufacturers Serum Institute of India have reported vaccine efficacy of 53.28% against symptomatic disease if the second dose was given in less than six weeks of the first dose and 78.79% if the second dose of the vaccine was administered after an interval of more than 12 weeks.[17] Accordingly, the manufacturers have recommended a schedule of two doses (0.5 ml) to be given intramuscularly into the deltoid muscle at an interval of 4–12 weeks.

Research papers of phase I/II/III efficacy trials of ChAdOx1 nCoV-19 in the United Kingdom, Brazil, and South Africa, against symptomatic disease caused by SARS-CoV-2 have found that individuals who received the second vaccine at an interval of more than 12 weeks after the first dose had 2-fold higher antibody titers as compared to those who received the second dose within 6 weeks. The vaccine efficacy after 2 standard doses was found to be 81·3% (95% CI, 60·3–91·2) when the two doses were spaced more than 12 weeks apart as compared to 55·1% (95% CI, 33·0–69·9) when the second dose was given within 6 weeks. The trials have also reported that even a single dose of vaccine provides 76%, (95% CI, 59·3–85·9) protection against symptomatic COVID-19 diseases in the first 90 days of initial vaccination.[18,19] ChAdOx1 nCoV-19 has been introduced in many countries; however, the regimen with regards to interval between two doses have been variable between countries. Australia has adopted an interval of 12 weeks between two doses, Spain and India has increased the dose interval to 12–16 weeks, whereas, UK has recently decreased the dose duration from 12 to 8 weeks in individuals more than 50 years.[20–23] As the virus continues to ravage the globe only time will tell which country's policies were successful in combating this deadly disease.

The World Health Organization in its interim guidelines issued on 10th February 2021 have reported the efficacy of AZD1222 vaccine against symptomatic SARS-CoV-2 infection to be 63.09% (95% CI, 51.81–71.73) irrespective of the dose interval. However, it also acknowledges that longer dose interval increases the vaccine efficacy. Therefore, based on evidence, the WHO has recommended an interval of 8–12 weeks between two doses.[24]

Discussion and recommendations

Following the accord of regulatory approval by DGCI for emergency use of ChAdOx1 nCoV-19 (AZD1222) vaccine in India, the key question for the decision-makers to answer before the rollout of the vaccine pertains to the optimal dose interval. The answer to the question can be based on two criteria, that is, the impact of the interval between the two doses on the overall protection offered by the vaccine and the degree of risk of infection in the interval between the two doses which can be either due to waning of the effect of the first dose or due to incomplete/inadequate protection provided by a single dose. The currently available scientific literature indicates that a 12 weeks interval between two doses provides better protection, without compromising protection in the intervening three-month interval between the two doses. A single standard dose of ChAdOx1 nCoV-19 has been shown to provide 76% protection against symptomatic COVD-19 in the first 90 days after vaccination, without evidence of waning of protection during this period.[19] These facts indicate that the second dose can be conveniently delayed without comprising the protection achieved from the first dose. However, in the present scenario where several SARS-CoV-2 virus variants are being reported from different countries including India, implications of effectiveness against the mutant variant (as vaccines may show less effectiveness against the mutant variant) and threats of emergence of escape mutations needs to be borne in mind.[25] Hence, with the emergence of B1.617.2 variant of concern, to provide maximum protection United Kingdom has reduced the dose interval in the most vulnerable groups (more than 50 years) from 12 to 08 weeks.[23]

COVISHIELD vaccination drive was started in India on 16th January 2021 with administration of two doses at an interval of 4 weeks. But, considering evidence that longer interval between two doses of COVISHIELD provides better protection, GoI after extensive deliberations issued a notification on 22nd March 2021 for the administration of the second dose between 6 and 8 weeks but not later than 8 weeks after the first dose.[26] Recently, on 13th May 2021, GoI further increased the dosing interval to 12–16 weeks.[22] Globally, there are insufficient data regarding the effectiveness of vaccines against the virus variants and early data from few studies have suggested less effectiveness of vaccines (Novavax, Johnson & Johnson, AstraZeneca, Pfizer-BioNTech, and Moderna) against the B.1.351 variant.[25] Considering that efficacy of a single dose of ChAdOx1 nCoV-19 vaccine falls to 31% after 12 weeks,[19] circulation of mutant variants would increase the threat to single dose recipients especially the vulnerable groups. Today, India has enough experience and scientific wherewithal to conduct vaccine efficacy studies in its own ethnic population rather than resorting to frequent deviations from recommended protocols based on data from the western world.

In light of, existing threat of circulating mutant SARS-CoV-2 virus variants and lack of clear evidence with regards to optimum dose interval, ***at this juncture it would be prudent to continue with vaccine protocols based on trails and administer two at an interval of 12 weeks***. Simultaneously, studies should be conducted in Indian population to better understand dynamics affecting immune response in vaccinated individuals, this would facilitate formulation of policies to ensure optimal vaccine protection and mitigation of COVID cases in India. In present times, with second wave showing signs of ebbing and an impending threat of a third wave, the need for a sound vaccination policy based on robust scientific evidence preferably emanating from Indian population is the only visible refuge for tiding over this pandemic.

Disclosure of competing interest

The authors have none to declare.

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