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Heterologous Prime-Boost COVID-19 Vaccination

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Abstract:

The prophylactic intervention is the ideal to fight against infectious diseases, the vaccination regimen for COVID-19 is yet still studied. The vaccination procedure requires experimental exams on different age groups to observe the immunity in which heterologous prime-boost research studies were shown to promote Th-1 response and T-cell reactivity with first dose viral vector vaccine following the second dose of mRNA vaccine. This regimen triggered an immune response which indirectly implies the protection capacity of the combination regimen against the virus. All in all, by doing research to find new findings can be new approaches for improving and developing COVID-19 vaccination to overcome the pandemic.

Keywords **—COVID-19, Heterologous prime-boost COVID-19 vaccination, reactogenicity**

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I. INTRODUCTION

Coronavirus Disease 2019, known as COVID-19 are named for Coronaviruses the crown-like spikes on their surface. The current scientific consensus is that the virus is most likely of zoonotic origin (1, 2). On 31 December, 2019, it was reported that there was an outbreak of COVID-19 from Wuhan, China (3). Eventually the disease has spread globally since then. As a result, COVID-19 is considered as highly transmissible. Regarding the outbreak, quarantine is used for anyone who is in contact with someone who is infected with the SARS-CoV-2 virus that would then cause COVID-19, despite the presence of the symptom or not (4, 5). The virus is spreaded through respiratory droplets produced by coughing or sneezing from any individuals (6). The safest way to maintain socially distant is to isolate oneself from others, Quarantine. This is to inspect whether a person is already the carrier or not. In this case, it means staying at home for up to 14 days (7). World Health Organization (WHO) stated that vaccines were the only way to fight against COVID-19 (8).(9) Variety of vaccines manufactured differently are developing and are launching consistently (8). Furthermore, COVID-19 vaccines in the category of four are available. Vaccines are differentiated by using parts of germ triggering the immune system or gene providing the cell to produce proteins specifically (10-13). This review aimed to hightlight the efficacy of the heterologous prime-boost COVID-19 vaccination regimen. Also providing the information ragardingreactogenecity data of heterologous ChAdOx1 nCoV-19 and BNT162b2 prime-boost vaccination.

II. COVID-19 VACCINES

The magnitude of COVID-19 pandemic outbreak has globally overwhelmed healthcare systems (14). Governments around the world prioritize vaccine research againsting the virus. Approximately 60 vaccine candidates are currently in clinical trials while 13 of them are in clinical trials in later stages (15-18). Whilst the constant drop in antibody timers for vaccinated individuals, the leading COVID-19 vaccines showed that there are SAR-CoV-2

protections available (19, 20). Nonetheless, the public-service are concerned about the effectiveness ,and protective measures' duration by vaccines in the early generation.

Typically with emergency vaccines, the currently developing majority of COVID-19 vaccines have advantages and disadvantages. Specifically, mRNA vaccines namely, BNT162b2 and mRNA-1273 have demonstrated that they could prevent infection from SARCoV2 (20-25). The main problem of mRNA vaccines is the cost from harsh cold chain requirements and the additional time (25). On the other hand, inactivated vaccines and protein-based vaccines demonstrated less side effects. Nonetheless, they lack more immunogenicity than mRNA vaccines. The BIBP-CorV, inactivated vaccine, and ZF2001, recombinant vaccine, induced weak T cell responses (26).

Alternatively, while CanSino, Ad5-vectored vaccines, has strong T cell responses, they are low in Nab response (27-32). The difference in these vaccines will be increased by the time they are being approved for large-scale uses. Vaccines for COVID-19 are developing that result in a paradigm shift in the developing process. Because of this, steps of developing vaccines are performed to save time for further emergency use. As a result, multiple formulations and platforms proceeding the COVID-19 vaccine have been increasing together with varieties progressing to early stages of clinical trials. Referring to paradigm shift, the abundance of COVID-19 vaccine candidates could be used to test for strategies for heterologous prime-boost vaccines to be able to obtain more effective immune responses, and improve profiles of safety (33-36). Hence, the research satisfies needs and could contribute to public health policies formation.

III. HETEROLOGOUS PRIME-BOOST COVID-19 VACCINATION: INITIAL REACTOGENICITY DATA

In fact, the highly desired vaccination is Heterologous prime-boost COVID-19 because it allows programmes of vaccines to avoid shortages, meet demand quicker, and supply stocks that could reduce vaccine rollout speed (33, 37, 38). The advice given by some countries stated that people who received ChAdOx1 nCoV-19 Vaxzevria vaccine (AstraZeneca) should be vaccinated with other vaccines that have commonly alternatives such as BNT162b2 (BNT) COVID-19 vaccine (Comirnaty, Pfizer-BioNTech) (37, 39-42). The safety of these vaccines are not yet to be studied. Study from the UK compared the difference in ChAdOx1 and BNT vaccines permutation at the time interval of 28-day and 84-day prime-boost intervals (37). Individuals with or without mild-to-moderate comorbidity are between the ages of 50 and 70 who are recruited from eight sites of study (37). The study trial steering committee following the consultation are pleased to introduce the preliminary data on reactogenicity and safety following with the outcome of primary immunology which is expected to be available in June 2021 (37, 43). The data has systemic symptoms reported from participants in seven days after prime and boost vaccinations which they were given randomly every 28 days (37, 43). Furthermore, in order to check for dangerous changes in haematology levels, and biochemistry, researchers have evaluated a hundred of participants before the prime does on the 28th day, and the 7th day post-boost, then grade their results by using FDA which is modified to obtain risk (43). Due to not powered for reatogeneicity of the stuudy, every analyse is descriptive with reported endpoints as perentages, frequencies and difference between heterologous and homologous vaccine schedules, and 95 percent Cis, confidene intervals (43).

Comparing their homologous counterparts, the results have greater systemic reactogenicity followed by the booster with fever reported by 34 percent of 110 recipients of ChAd for prime and BNT for booster compared to ten percent of 112 recipients (43). About thirty-one percent of BNT for prime and boost recipients reported feeling feverish, though only twenty-four per cent of the BNT for both prime and boost recipients reported feeling feverish (43). Headache, tiredness, shivers, joint pain and muscle ache are all experienced similarly. No hospitalisations associated with symptoms and the majority of the rise in

reactogenicity which occurred within 48 hours of vaccination (43).

Paracetamol could help with the effects of vaccines though it is not encouraged to dose as a measure of prevention. Thirty-six percent of 112 recipients of ChAd for both prime and boost reported usage of paracetamol in the 48-hour post-boost vaccination period. Forty-one percent of 110 recipients of ChAd for both prime and boost reported usage of paracetamol in the 48-hour post-boost vaccination. Labs reported all grade 2-severe adverse events on both heterologous and homologous vaccination schedules, and there were no platelet issues among all groups on day 7 post-boost (43).

As what was measured by the number of participants who used paracetamol after receiving the boost does, the systemic reactogenicity increases with heterologous vaccines schedules compared to homologous vaccine schedules. The datas have been accessed from participants at the age of 50 years and older (44). It is more reactogenic at younger age groups which gives concerns with ChAd's first dosage before thrombotic thrombocytopenia (43, 45).

Once a completed immunogenicity and safety results of heterologous schedules of prime-boost are available, those data indicate that the two heterologous vaccine schedules used in the trial have few disadvantages in the short run. Paracetamol together with Routine post-immunisation prophylaxis is currently being studied in Com-COV participants who receive prime and boost vaccines at the intervals of 12-week (37, 43). Nevertheless, it is reassured that all reactogenicity symptoms were transient and the biochemistry, and haematology data available revealed no cause for any concern. Greater number of studies are done to evaluate the heterologous prime-boost vaccination schedules which should be appropriate and incorporate vaccines produced by Novavax and moderna. These studies are considered critical as they help to address the use of mixed COVID-19 vaccines schedules appropriately (37, 43).

According to the randomised-control trial performed in 25 hospital in Russia Russia was studied participants (18 years and older) that had negative SARS-CoV-2 PCR and IgG and IgM tests had yet to be exposed to infectious disease within the 14 days enrollment. And the participants had yet to receive another vaccination 30 days enrollment(46-48). The participants were given intramuscular administration (0.05 mL/dose) of the first dose (rAd26) and 21 days interval before the second dose (rAd5) which both contain the full length SARS-CoV-2 glycoprotein S gene (46). First result measure was participant's proportion of participants with COVID-19 infection which was detected by PCR on the 21th day followed by the first dose. Every analysis excluded the participants who had placebo or vaccine in two doses. All participants were evaluated for serious events (46-48).

Between the 7th of September and 24th November, 2020, 21977 of adults were assigned randomly to receive either a placebo (n=5476) or the vaccine (n=16501) (46). The first analysis of the results included 19866 participants receiving the vaccine or placebo for two doses (46). The results showed that vaccine efficacy was 91.6% which was confirmed by 16 of the 14964 participants within the group of vaccine and 62 of the 4901 in placebo groups. Of the 16427 participants in the vaccine group, 45 experienced serious circumstances compared to 23 among the 5435 participants within the group of placebo (46). None of the serious circumstances was related to vaccination reported by data independently monitored by the committee. It was discovered that four deaths had occurred during the study, 3 of 16427 participants in the group of vaccine and 1 of 5434 participants in the group of placebo, neither of them were vaccine associated. Therefore, 3 trials of Gam-COVID-Vac illustrated that this vaccine regimen was 91.6% efficacy for COVID-19 (46).

Reactogenicity study of the T-cell response of 25 participants out of 46 who get ChAdOx1 as their first dose followed by an 8-week booster dose of BNT162b2 against B.1.1.7, B.1.351, and B.1.617 have reported the reactogenicity as similar as the previous report (49, 50). Also, the neutralising antibody level was at the highest peak after two weeks of the second dose. The

neutralising antibody of heterologous prime booster (ChAdOx1/BNT162b2) was 3.9 higher than the heterologous prime boost of BNT162b2 against alpha variants (B.1.1.7). Whereas, in the variant of concern B.1.351 seemed to be opposite (2-times lower) and was roughly similar with B.1.617 variant (49). Also, CD4+ and CD8+ T cells were activated to SARS-Cov-2 spike protein 2 week after the second dose. This ChAdOx1/BNT162b2 regimen was related to the triggering of cell-mediated (T-cells reactivity) and humoral immune response (B-cells reactivity) (49). Interestingly, the plasma neutralising antibody of all participants showed a potency to neutralise all 3 studied variants of SARS-CoV-2 (49, 51, 52). This result can be explained that the ChAdOx1/BNT162b2 regimen is as protective as the homologous vaccinations (49-52).

IV. HETEROLOGOUS VACCINATION REGIMENS INDUCE IMMUNE RESPONSE IN MICE

The full-length of SARS-CoV-2 spike protein SRNA together with ChAdOxl vaccines immunogenicity was analysed after vaccination by using combinations of modalities of the vaccine (53). The study illustrated solid antibody reactions neutralising antibody ny a high-title antibody followed by heterologous vaccinating regimens (53). Responses of cellular immunes are influenced by cytotoxic T cells which are factor-α (TNFα) tumour crossing,CD4+ T antigenic cells with a Th1 phenotype, and interferon-α (IFNμ) (53). The findings support clinical trials' needs for evaluating immunisation regimens which use alternative vaccine delivery methods (53).

The study illustrates two doses of heterologous vaccination regimens which produce elevated antibody responses more than regimens of single-dose. Vaccination of heterologous prime-booster followed by neutralising titres were comparable or greater than vaccination of homologous prime-booster together with the viral vectors. Moreover, Th1+ CD4 T cells predominate and cytotoxic T cells follow a heterologous vaccination regimen in mice (53). The response performed better than the response that was induced by homologous vaccination regimens (53). Referring to the findings, clinical trials that used alternative vaccine technologies should be conducted.

CONCLUSIONS

In conclusion, the several clinical studies of heterologous prime-boost research were shown to promote Th1- response as well as T-cell reactivity. Also, combination consisted of the adenovirus-based vaccine as a primary dose followed by mRNA, protein subunit or inactivated vaccines exhibit the potential to promote the increase of neutralising antibody level. However, this result on triggering immune response may not directly imply the protection capacity of the combination regimen against SARS-CoV-2 infection. Since long-term clinical studies of the lasting effects of immune response are still required. Nevertheless, these findings can be new approaches for improving and deploying COVID-19 vaccines to overcome the unprecedented Covid-19 pandemic.

V. DISCUSSION

The exceptional efforts and the pandemic began in developing vaccines which are effective with subsequent mass immunisation that have shown the practicalities for international campaigns of vaccination (8). Approximately there are 20 vaccines which are currently undergoing an evaluation of 3 phase clinical trials and a number of vaccines demonstrated effectiveness as a result, few countries want emergency licensure (54-58). Nevertheless, there is no study published to examine the mix of modality vaccines and their safety (57, 58). In fact, the given current state of global vaccination initiatives provide scenarios in which an individual receives the booster and prime dose from vaccine types and various manufacturers (58). Currently, the preclinical study has examined humorous immune reactions and cells after saRNA and ChAdOx adenoviral vector have been vaccinated in heterologous and homologous combinations which supports the evaluation requirement heterologous prime-boost regimes in a clinical test strongly (53). Every prime-boost regimen produced higher SARS-CoV-2 antibodies of spike-specific significantly together with the

high avidity and the capacity of single vaccine neutralisation (14, 53). Regimens of heterologous elicited most robust responses of antibody with neutralizing titre which is greater or lesser comparable to obtained vaccination of homologous with ChAdOx1 nCoV-19 (37). Conversely, ChAd and homologous saRNA brought out more robust responses of antibodies than regimens of single doses than the last study (14). This study has demonstrated in nonhuman primates that homologous vaccination with ChAdOx1 nCoV-19 cause diseases protection which is recently greater in hamsters which single immunisation together ChAdOx1 nCoV-19 protection against the disease which is caused by the variants of concern B.1.1.714 and B.1.351 (59-61). In fact, this regimen in human clinical trials demonstrates efficacy against SARS-CoV-2 disease in later stages of trails. Alternatively, the data in the elders showed the effectiveness of the vaccine at 80.4% followed by the ChAdOx1 nCoV-19 dose. Rhesus macaque studies established a role for $CD8^+$ T cells in disease protection and neutralising antibodies although clinical trials have yet to establish clear correlations of protection. Human studies showed that neutralising T cells and antibodies play a significant part in the prevention of disease which is severe and COVID-19 recovery (62, 63). Modalities of vaccine of both resulted in an increase in antigen-specific T cells amplified in heterologous regimens as well (53). Majority of IFN ELISpot responses were directly in opposition to the S1 Protein spike, specifically against the (317 amino acids), which lacks the receptor-binding domain (RBD) (53). Cytotoxic T cells dominated the response of cell-mediated cells. T-cell responses were less numerous and frequent than the CD8+ T-cell responses that shows subsequent enhancement of respiratory disease and potential of antibody-dependent enhancement are caused by the diminished Th2-type lung immunopathology (53). Long-term COVID-19 protection will almost definitely necessitate a widespread immune response (humoral and cell-mediated). It is unknown whether elevated antibody titres, as evaluated in this report, result in longer-term protection with a broader range of humorous responses following heterologous vaccination schemes (64-66). A restricted global supply and the logistical hurdles of providing vaccines in an ever-changing landscape of mass immunisation programmes highlight the need of obtaining data on vaccine modality mixing. Clinically, the presence of an altered or diminished reactogenicity pattern in the mixed modality systems and, most crucially, the potential to promote disease protection or additional transmission will have to be assessed (33, 37, 38, 47).

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