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HETEROLOGOUS PRIME-BOOST VACCINATION FOR COVID-19

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ABSTRACT

With the ongoing of the covid-19 pandemic, which has already spread to over 222 nations worldwide, covid-19 has become a major dangerous respiratory illness that causes about 219 million cases and 4.55 million fatalities globally. As a result, several vaccines are being developed to assist ease the issue. In order to cure this condition as soon as possible, the approach of combining several types of vaccinations is applied for individuals who develop an adverse allergic response to the first vaccine and used as a booster or third dose vaccination. Many studies have shown that heterologous vaccination using a viral vector vaccine as the first dose and an mRNA vaccine as the second dose results in better protective immunity. Similarly, employing a viral vector vaccine as a prime dose followed by an inactivated vaccine resulted in a stronger immune response. However, the initial vaccination with an mRNA vaccine and the second immunization with a viral vector platform result in a reduced level of protective immunity. For safety concerns, heterologous prime-boost immunization is also approved as a safe option, showing only minor side effects. In conclusion, the mix-and-match vaccine approach can elicit greater immunity depending on the sequence of vaccine type immunization.

Introduction

Over an average day, there are now 141 Covid fatalities in Thailand, with around 10,820 cases, and 4,547,800 deaths around the world, with 219,460,000 cases (1). Due to the present COVID-19 crisis, COVID-19 vaccinations are in great demand across the world to help relieve affected infections. Despite the fact that numerous vaccinations have been developed and researched throughout many countries to help alleviate this epidemic, people still stand a significant risk of developing an allergic response after receiving a vaccine. As reported in the USA, December 14-23, 2020, after receiving the first dose of the Pfizer-BioNTech COVID-19 vaccine, a proportion of patients continue to have allergic responses, including anaphylaxis.(2)

Furthermore, multiple new results regarding the third vaccination to boost the immune system are constantly being developed for people who have had two doses of vaccinations but whose immunological numbers have not yet improved, which in some cases, their immunity has even fallen.(3) Accordingly, several nations are seeking more effective vaccines in order to prevent the spread of the Covid-19 pandemic.

As a result, several nations are devotedly attempting to study and discover the most efficient approach to completely eliminate this virus by testing with different types of vaccines and even combining vaccines. Having a host of previous successful studies of mix and match vaccination such as a mixture of recombinant HIV-1 proteins, the recently authorized Ebola vaccine and vaccines for malaria as the inspiring concepts (4), present researchers tried adapting the similar strategy and found that ,to maximize the benefits of vaccination, employing a heterologous prime-boost strategy in which different combinations of the four types of leading COVID-19 vaccine candidates can lead to the efficient solution that we all desired.

While more and more research on combining Covid-19 vaccines are being held, many studies found that mixing Oxford-AstraZeneca, a viral vector vaccine which uses a harmless virus to trigger the immune system to create antibodies to fight off an infection by SARS-CoV-2, which is the virus that causes COVID-19, as a prime dose with the Pfizer-BioNTech COVID-19 vaccine, a mRNA vaccine

which uses messenger ribonucleic acid (mRNA), a molecule that provides cells with genetic instructions, for making proteins that are needed for numerous cellular functions in the body, including for energy and immune defense, as a boost can be one of the most efficient solutions.(5) In this review, we discussed a mix and match of AstraZeneca and Pfizer and inversely Pfizer and AstraZeneca Covid-19 vaccines.

Current approved COVID-19 vaccines

During the crisis of COVID 19 pandemic, several vaccines have been designed and developed in order to eliminate the spreading. Accordingly, various types of vaccines have been approved and authorized for emergency use by the FDA. These types of approved vaccines against SARS-CoV2 include inactivated vaccine, viral vector vaccine, and mRNA-based vaccine.(6)

mRNA vaccines, the first type of vaccination to be licensed, function by using the information in genes to create a blueprint for making proteins. Using this mRNA blueprint, cells produce the viral protein. As part of a normal immune response, the immune system recognizes that the protein is foreign antigen. After the recognition, the immune response creates the protective barrier such as producing specialized defensive proteins called antibodies. Antibodies help protect the body against infection by recognizing individual viruses or other pathogens, attaching to them, and marking the pathogens for destruction. Vaccines categorized as mRNA based platforms are Pfizer (BNT162b2) and Moderna (mRNA-1273). (7)

Inactivated vaccines were the first to be produced. An inactivated vaccine uses a strain of a bacteria or virus that has been killed or modified with heat, radiation, or chemicals so that it is unable to replicate. This dead form of the virus or bacteria is then injected into the human body. Because It cannot cause disease, it is therefore suitable for those with individuals who have compromised immune systems. Inactivated vaccines can trigger a strong immune reaction, but it is usually not as strong as what other vaccines can produce. Due to this, a person may need booster shots to ensure ongoing protection. (8)

Viral vector vaccines modify another harmless virus and use it as a vector to deliver genetic information of SARS-CoV2 into human host cells. Similar to the mRNA vaccine, host cells produce SARS-CoV2 spike protein and trigger the immune system. Adenovirus is used as a viral vector to produce ChAd-Ox1-S vaccine (AstraZeneca). (9)

In order to design the most effective vaccine against several new viral variants, new candidate vaccines are under investigation. These included new types of vaccines such as protein-based vaccines, new generation of available vaccines and also the strategies of mix and match vaccines.

Heterologous prime-boost vaccination

1. Prime with viral vector vaccine and boost with mRNA vaccine

Several studies demonstrated that heterologous immunization generates improved immunity against SARS-CoV2 virus when using viral-vector vaccine as a first dose and mRNA vaccine as a second dose. A study conducted in the UK with 830 participants reported that the concentration of SARS-CoV2 anti-spike IgG in patients receiving first vaccination with ChAd and second vaccination with BNT (ChAd/BNT = 12,906 ELU/ml) was extremely higher than homologous ChAd vaccination(ChAd/ChAd = 1,392 ELU/ml). The level of antibody was measured at day 28 post-boost vaccination. While the antibody level is slightly but not significantly different from the individuals who receive full BNT vaccination (BNT/BNT = 14,080 ELU/ml). Moreover, greater cellular immune response as measured by ELISpot was found higher in ChAd/BNT than ChAd/ChAd immunization. (10)

This result correlated to a second study in which heterologous ChAdOx1-S and BNT162b2 vaccination provides better humoral and cellular immunity than homologous ChAdOx1-S vaccination. After BNT162b2 was given as a second dose 8-12 weeks after a first dose of ChAdOx1-S, geometric mean titres (GMT) of IgG specific to the SARS-CoV-2 RBD were significantly higher in the interventional group, as were the number of antibodies against SARS-CoV-2 spike protein. The study also found that using BNT162b2 as a second dose in a heterologous scheme improves cellular immunity responses obtained after an initial dose of ChAdOx1-S, whereas using second doses of ChAdOx1-S in homologous schedules failed to improve cellular immunity responses obtained after an initial dose. Nonetheless, participants in heterologous vaccinations reported a rise in systemic reactogenicity following the boost dosage, notably in a self-reported sensation of feverishness. However, only 1.75 percent of those adverse events were classified as serious by the participants. (11)

Another research with 216 immunocompetent people was performed in Germany, with 97 receiving heterologous immunization with the ChAdOx1-vector and mRNA boost (vector/mRNA). The findings reveal that following vaccination, spike-specific IgG was

produced in 215/216 people, and leukocyte counts, including granulocytes, monocytes, and lymphocytes, as well as significant lymphocyte subpopulations including CD4- and CD8 T cells, and B cells, did not differ between the groups. IgG levels following heterologous immunization were comparable to those in the homologous mRNA vaccine group, but were substantially lower after homologous vector vaccination. This difference was also seen in the activity of neutralizing antibodies, which was measured using a surrogate neutralization test. While the majority of people in the vector/mRNA and mRNA/mRNA groups had 100% inhibitory activity, the vector/vector group had substantially less. After that, when comparing reactogenicity after subsequent immunization, homologous vector boosting resulted in much less local and systemic reactions. Boosting with an mRNA vaccine, on the other hand, was less well tolerated, and the range of local and systemic adverse effects for both vector- and mRNA-primed people was quite comparable. (12)

In the fourth research, 463 people were randomly allocated to four groups with a 28-day prime-boost interval and 367 to groups with an 84-day prime-boost interval in Palestine. We found an increase in systemic reactogenicity after the boost dose reported by participants in heterologous vaccine schedules compared to homologous vaccine schedules in 40 (36%) of 112 recipients of ChAd for both prime and boost, 63 (57%) of 110 recipients of ChAd for prime and BNT for boost, and 48 (41%) of 117 recipients of BNT for both prime and boost. Following the boost dosage, both heterologous vaccination regimens produced more systemic ability than their homologous versions. Immunogenicity data for heterologous prime-boost vaccination schedules, on the other hand, imply that two heterologous vaccine regimens in this experiment may have some short-term drawbacks. Chills, tiredness, headache, joint discomfort, malaise, and muscular soreness all showed similar increases. (13)

Another research of 340 health-care professionals in Germany found that heterologous ChAdOx/BNT booster immunization was well-tolerated generally, with reactogenicity close to homologous BNT/BNT vaccination. When compared to homologous BNT/BNT vaccination with three week vaccine intervals, the heterologous ChAdOx/BNT immunization regimen with 10-12 week vaccine intervals is well tolerated and somewhat more immunogenic. Furthermore, antibody responses in homologous BNT/BNT immunized subjects were comparable to heterologous ChAdOx/BNT immunized people three weeks following boost vaccination. When comparing heterologous ChAdOx/BNT boost to homologous BNT/BNT boost, IgG avidity maturation was somewhat greater after heterologous ChAdOx/BNT boost. Additionally, after homologous and heterologous prime-boost vaccination, surrogate virus neutralization test (sVNT) titers were similar. Systemic responses were most common following prime ChAdOx immunization, were less common after homologous BNT/BNT booster vaccination, and were least common after heterologous ChAdOx/BNT booster immunization. However, compared to homologous boost vaccines, 80 percent of those who received a heterologous prime-boost with ChAdOx/BNT experienced tiredness and other systemic symptoms, a 40-fold increase. (14)

Finally, the huge research was performed in Denmark, with approximately 5.5 million participants were recruited. The age of the participants ranged from 45 to 46 years old, with an equal number of males and females. At 0-13 days and 14 days following the ChAdOx1/mRNA vaccination schedule, adjusted Vaccine effectiveness (VE) estimations of 43 percent and 50 percent were observed, respectively. When compared to two doses of the ChAdOx1 vaccine, immunological investigations show that theChAdOx1/BNT162b2 vaccination schedule is linked with greater humoral immune responses and stronger anti-SARS-CoV-2 spike T cell responses. Also, during the research period, no COVID-19-related hospitalizations or fatalities occurred among those who got the ChAdOx1/mRNA vaccination regimen. This suggests that combining the ChAdOx1 with an mRNA vaccination protects against serious consequences. (15)

To summarize, the findings from six different experiments and studies show that a combination of AstraZeneca (ChAd) as a dose and Pfizer (BNT) as a prime is an efficient alternative, evidenced by the the amount of antibodies against SARS-CoV-2 spike protein being significantly higher than homozygous matches,which indicates a positive feedback toward us, humans. (11)

2. Prime with mRNA vaccine and boost with viral vector vaccine

In contrast to the heterologous immunization results described above, vaccination using mRNA vaccine as an initial dose and viral-vector vaccine as a booster induce weak protective immunity. In the United Kingdom, 830 people were enlisted and randomly assigned to a trial, with 463 of them receiving a 28-day prime-boost interval. The geometric mean concentration of SARS-CoV-2 anti-spike IgG in individuals primed with BNT was 14080 ELU/mL in the homologous group (BNT/BNT) and 7133 ELU/mL in the heterologous group (BNT/ChAd) at 28 days post boost vaccination. Participants who received a ChAd boost after receiving a BNT prime (BNT/ChAd) exhibited vastly greater SARS-CoV-2 anti-spike IgG than those who received a ChAd prime (ChAd/ChAd). Aside from that, cellular immune responses in the BNT vaccine-containing regimens were all at least as strong as those in the ChAd/ChAd group, with BNT/ChAd exhibiting the most proliferation of vaccine-antigen responsive T cells in the peripheral circulation at 28 days post boost. The immunological findings provided here, together with the observation that T-cell ELISpot readouts are comparable between schedules, provide comfort that ChAd/BNT and BNT/ChAd are viable scheduling alternatives. In contrast to prior non-

blinded and non-randomized trials, the results revealed that the 28-day ChAd/BNT schedule was more reactogenic than the ChAd/ChAd schedule. The change in the prime-boost interval might be to blame for the disparity. (10)

To summarize, scientists discovered that in heterologous vaccination schedules, systemic reactogenicity increased following the boost dose, compared to homologous vaccine schedules. (13)

3. Prime with viral vector vaccine and boost with inactivated vaccine

Apart from using mRNA vaccine, the effectiveness of heterologous vaccination with combination of viral-vector platform and inactivated vaccine was also investigated. However, there is only one study conducted in India in order to follow up 18 patients mistakenly received heterologous vaccination. These participants received AstraZeneca's ChAdOx1-nCov-19 (Covishield) as a first dose and inactivated whole virion BBV152 (Covexin) as a second dose. The humoral immune response in the heterologous group was found to be considerably greater than in the homologous groups. In the peripheral blood, both groups had a similar percentage of major lymphoid cells such as B-lymphocytes, Natural Killer cells, and CD3+ T cells. This points to no significant differences in generalized cellular immunity between the vaccinated research groups. However, the percentage of CD8+ T cells in the heterologous group was significantly higher than another group, indicating that they had more cytotoxic activity. The Research shows that immunizing with a heterozygous combination of an adenovirus vector platform-based vaccine followed by an inactivated whole virus vaccine is both safe and effective, outperforming two rounds of homologous vaccination with the identical vaccines. (16)

Side effects from the mix and match

No mix-and-match trials have yet reported severe side effects. In a research done with 463 participants in Palestine, the results showed that fever was reported by 47 of 114 BNT for prime and ChAd for boost patients, compared to 24 of 112 BNT for both prime and boost recipients. Chills, tiredness, headache, joint discomfort, malaise, and muscular soreness all showed similar increases. Apart from that, no hospitalizations were required owing to requested symptoms, and the majority of the rise in Reactogenicity occurred within 48 hours of vaccination, indicating that mixing vaccines elicited no more side effects than two doses of the same vaccine. (13)

But this wasn't the case in the study in which heterologous ChAdOx1-S and BNT162b2 vaccination and homologous ChAdOx1-S vaccination are compared showed the result of an increase in systemic reactogenicity after the boost dose reported by participants in heterologous vaccines particularly in a self-reported feeling of feverishness. However, only 1.75% of the adverse events were self-reported as severe. Similarly, in the third study reactions were mild or moderate with injection site pain, induration, headache, and myalgia the most commonly reported adverse events. No serious adverse events were reported. (11)

Overall, The results show that people who had the AstraZeneca vaccine first followed by the Pfizer-BioNTech vaccine, or the other way around, had more reactogenicity, side effects such as fever, chills, headache, muscle fatigue and joint pain, compared with people who had two doses of one type of vaccine. Nevertheless, it was noted that no one needed to be hospitalized because these symptoms were short-lived, but add that this data was from people 50 years or older, and that symptoms from mixing vaccines could be more severe in younger people. Accordingly, Scientists are continuing to analyze combinations of the AstraZeneca, Moderna's mRNA or Novavax vaccines and further studies are being held to investigate long-term side effects.(13)

Conclusion and future perspective

The effectiveness of the heterologous prime-boost vaccination highly depends on the sequence of variance type used for the vaccination. Using viral vector vaccine as a first dose followed by the mRNA vaccine or the inactivated vaccine result in stronger and more robust immune responses than homologous vaccination, while using mRNA as a first dose with viral vector as a second dose leads to diminished immunity. Since this vaccination strategy can help in improving vaccination operations in nations where vaccine supplies are in short supply, further studies are required for the several types of vaccine combination such as inactivated vaccine followed by mRNA vaccine or inactivated vaccine followed by viral vector vaccine. Moreover, even if no severe side effects are reported after the heterologous prime-boost vaccination, more studies are still required to assess the long-term side effects.

The next generation of coronavirus vaccines will almost likely target several coronavirus variants, with distinct vaccinations focused on each variety. Combining these vaccinations would offer widespread collective immunity while also making it more difficult for variants or new ones to propagate. Mixing doses might provide us with even more options for a booster program, while also assisting nations who have a long way to go with vaccine rollouts and may be suffering supply issues. However, like with past vaccinations, additional study is necessary to be done on a regular basis.

Table 1. Heterologous prime-boost research

Research group	Type of heterologous vaccination	Study location	Number of participants	Result
Alberto M Borobia	viral vector/mRNA	Spain	676	Greater than homologous viral vector
Tina Schmidt, 2021	viral vector/mRNA	Germany	216	Greater than homologous viral vector and comparable to the homologous mRNA
David Hillus, 2021	viral vector/mRNA	Germany	340	Greater than homologous viral vector and homologous mRNA
Mie Agermose Gram	viral vector/mRNA	Denmark	5,542,079	Greater than homologous viral vector
Xinxue Liu	viral vector/mRNA	UK	830	Greater than homologous viral vector while slightly lower than homologous mRNA
Xinxue Liu	mRNA/viral vector	UK	830	Greater than homologous viral vector but not greater than homologous mRNA
Rajni Kant	viral vector/inactivated	India	18	Greater than homologous viral vector and homologous inactivated

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