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Original article

Heterologous prime boost COVID 19 vaccination

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ABSTRACT

Heterologous prime boost vaccination is a primary vaccination with different vaccines, most often from different vaccine platforms. It combines the immunological properties of the different vaccines and thereby induces humoral, cellular and, in some cases, mucosal response.

For Covid prevention, it has been used in primary vaccination, due to safety issues and in boosters.

We have evaluated some articles reporting on the results of this type of vaccine, and demonstrating its usefulness.

1. Introduction – Definition

Heterologous prime boost vaccination consists of a primary vaccination with different vaccines, most often from different vaccine platforms. It differs from the "homologous" scheme, in which the same vaccine is administered twice in succession.

The objectives of heterologous prime boost vaccination are to combine the immunological properties of the different vaccines and thereby induce humoral, cellular and, in some cases, mucosal response. As regards vectored vaccines, they would avoid immunization against the vector.

In the context of Covid 19 vaccination, a heterologous scheme has been used in primary vaccination to major efficacy, due to safety issues and in boosters. It has also been used to avoid adverse effects or due to problems of vaccine availability.

Several studies evaluating homologous and heterologous vaccine schemes have been published:

Logunov et al. [1] presented an interim analysis of a randomised controlled phase 3 trial in Russia designed to assess the safety and efficacy of Gam-COVID-Vac (Sputnik V), a heterologous recombinant adenovirus (rAd)-based vaccine combining rAd26 and rAd5 vector-based COVID-19 vaccines. The prime-boost regimen was organized with a 21-day interval between the first dose (rAd26) and the second dose (rAd5), with both vectors carrying the gene for the full-length SARS-CoV-2 glycoprotein S. Interim analysis of the phase 3 trial of Gam-COVID-Vac showed 91.6% efficacy against COVID-19, and the regimen induced a virus-neutralizing humoral response in all participants, even those older than 60 years [1]. No further results have been published since the first paper.

Chahla et al. [2] studied the long-term humoral immune response of SPUTNIK V in naive and previously infected patients. Immune responses were analyzed using an anti-SARS-CoV-2-receptor-binding domain (RBD) ELISA, which showed excellent correlation with virus-neutralizing activity. One week after completing the vaccination scheme, antibody titers were present in 97.6% of volunteers. The group with previous SARS-CoV-2 infection showed median anti-RBD titer 4.6-fold higher after the first dose as compared to individuals in the unexposed cohort (460 vs 100 UI). The second SPUTNIK V vaccine dose further increased median anti-RBD titer in previously infected individuals compared to the control group (1300 vs 755 UI) at 28 days post-vaccination. These findings suggest that the first dose of SPUTNIK V in individuals pre-exposed to SARS-CoV-2 elicited a secondary immune response. The authors then separately evaluated the effect of previous SARS-CoV-2 infection on the levels of anti-RBD antibodies elicited by SPUTNIK V in 60, 90, and 180-days post vaccination. Six months after vaccination, anti-RBD antibodies had decreased and no significant difference was observed between median titers elicited in the two groups (naive and previously infected). These observations raise questions about long-term protection [2].

In July 2021, Dhashhordj et al. [3] collected plasma specimens from 196 Mongolian participants who were fully vaccinated with one of four COVID-19 vaccines: Pfizer/BioNTech, AstraZeneca, Sputnik V, and Sinopharm. Functional antibody testing with a panel of nine SARS-CoV-2 viral variant RBD proteins revealed marked differences in vaccine responses, with lower antibody levels and RBD angiotensin-converting enzyme 2 (ACE2) blocking activity induced by the Sinopharm and Sputnik V vaccines as compared to the AstraZeneca or Pfizer/BioNTech vaccines.

After reports of severe thrombotic events, several European governments recommended using AstraZeneca's ChAdOx1-nCov-

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19 (ChAd) only in individuals more than 60 years old, thereby leaving millions of ChAd-primed individuals with the choice of receiving either a second shot of ChAd or a heterologous boost with mRNA-based vaccines. Barros-Martins et al. [4] had a cohort of healthcare professionals monitor ChAd-primed immune responses before and 3 weeks after a booster with ChAd (n = 32) or BioNTech/Pfizer's BNT162b2 (n = 55) vaccine. They noted stronger humoral immune response and anti-SARS-CoV-2 spike T cell response against all SARS-CoV-2 variants following heterologous ChAd/BNT versus homologous ChAd/ChAd vaccination.

Liu et al. [5] reported data about the safety and immunogenicity of heterologous schedules with ChAd and BNT vaccines. Adults aged 50 years and older were randomly assigned (1:1:1:1:1:1:1:1) to receive ChAd/ChAd, ChAd/BNT, BNT/BNT, or BNT/ChAd, which was administered at either 28-day or 84-day prime-boost intervals. The primary endpoint was the mean ratio of SARS-CoV-2 anti-spike IgG concentration at 28 days after boost, when comparing ChAd/BNT with ChAd/ChAd and BNT/ChAd with BNT/BNT. The ChAd/BNT schedule was statistically superior to the ChAd/ChAd schedule in terms of the SARS-CoV-2 antispike IgG, humoral response and T cellular responses.

Pozzetto et al. [6] published a real-world observational study of healthcare workers (n = 13121). They observed that the heterologous ChAd/BNT combination conferred better protection against SARS-CoV-2 infection than the homologous BNT/BNT combination. While both combinations induced strong anti-Spike antibody responses, sera from heterologous vaccinated individuals showed stronger neutralizing activity, regardless of the SARS-CoV-2 variant.

In a trial with 417 participants, Janssen et al. [7] studied the interchangeability of mRNA vaccines with regard to 4 different vaccine regimens, using two vaccines: BNT162-B2 (Pfizer) and mRNA 1273 (Moderna). The regimens were Pfizer/Pfizer, Pfizer/Moderna, Moderna/Moderna, Moderna/Pfizer. They observed that as a second dose, the Moderna vaccine produced better immune response than the Pfizer vaccine, independently of the vaccine administered for the 1st dose.

Munro et al. [8] conducted a multicentre, randomised, controlled, phase 2 trial with 2898 participants of third-dose booster vaccination against COVID-19. They evaluated the reactogenicity and immunogenicity of seven different COVID-19 vaccines as third dose after two doses of ChAdOx1 nCov-19 or BNT162b2: NVX-CoV2373 (Novavax), BNT, VLA2001 (Valneva), a half dose of VLA, Ad26.COV2.S (Janssen), mRNA1273 (Moderna), CVnCov (CureVac), and a half dose of BNT. All of these vaccines showed boosted antibody and neutralising responses after a ChAd/ChAd initial course, and all except one after BNT/BNT [7].

Atmar et al. [9] studied the effect of a booster injection with one of the three vaccines (mRNA-1273 (Moderna), Ad26.COV2.S (Johnson & Johnson-Janssen), or BNT162b2 (Pfizer-BioNTech) after a complete covid 19 vaccine regimen in 458 participants. Homologous boosters increased neutralizing antibody titers by a factor of 4 to 20, whereas heterologous boosters increased titers by a factor of 6 to 73. Spike-specific T-cell responses increased in all regimens except homologous booster with Ad26.COV2.S.

2. Conclusion

These data illustrate the possibility of 'mixing' vaccines in primary vaccination, but not at random. We noted the interest of heterologous boosts, particularly after vaccination by vectorized vaccine.

Several questions remain unanswered: the place of other vaccine platforms (inactivated vaccines, subunits) in response to variants; the interest of heterologous boost with regard to mucosal response; and the place of heterologous boost vaccination in immunocompromised patients.

3. Disclosure of interest

The authors declare no conflict of interest.

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5. Authors' contributions

All authors contributed equally to this work.

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