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EDITORIAL

Editorial: Comparison of antibody and T cell responses elicited by BBIBP-CorV (Sinopharm) and BNT162b2 (Pfizer-BioNTech) vaccines against SARS-CoV-2 in healthy adult humans

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Abstract Vaccine development has become the main tool for reducing COVID-19 cases and the severity of the disease. Comparative analyses of adaptive immunity generated by different vaccines platforms are urgently needed. Multiple studies have compared different vaccines using similar platforms; however, comparative analyses of vaccines across different platforms are lacking. This Editorial provides a summary and commentary on the main findings reported in the observational and longitudinal study by Vályi-Nagy et al. (*Geroscience* 43:2321) that compared the adaptive (humoral and T cell-mediated) immune responses elicited by Sinopharm and BNT162b2 vaccines against SARS-CoV-2 virus among 57 healthy adult Hungarian volunteers.

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Vaccine development has become the main tool for reducing COVID-19 cases and severity of disease [1]. Several vaccine strategies have been developed that use different molecular platforms, namely nucleic acid-based, non-replicating viral vector-based, inactivated whole virus-based, or recombinant subunit-based vaccines [2]. Up to date, the World Health Organization (WHO) has granted emergency approval for the use of 10 vaccine [3]. Despite their differences, all these vaccines have reproducibly elicited a protective immune response against SARS-CoV-2 infections of significant magnitude in clinical trials [2]. Earlier studies on COVID-19 infections confirmed that virus invasion induces innate immunity [4]. Several studies have reported the production of antibodies with neutralizing capacities, along with broad cellular immune responses that help in clearance of the virus [5–10]. Effective protection against SARS-CoV-2 is thus mediated by both antibody-mediated humoral immunity and T cell-mediated cellular immunity [11].

Seven inactivated virus-based vaccines are in phase 1 or 2 clinical trials, with eight (2/3) in phase 3 and one in phase 4 [12]. The two inactivated vaccines most widely used are CoronaVac from Sinovac Research and Development Co. Ltd. (hereinafter Sinovac) and BBIBP-CorV from Sinopharm, from

the China National Biotec Group Co. and Beijing Institute of Biological Products (hereinafter Sinopharm). These two vaccines received the WHO emergency use grant [13]. Sinopharm Phase 3 clinical trials carried out in Argentina (Clinical Trial Identifier: NCT04560881) [14], Bahrain, Jordan, Egypt, and UAE (Clinical Trial Identifier: NCT04510207), (Registration Number: ChiCTR2000034780) evaluate the incidence of COVID-19 in individuals that have received two doses of the vaccine. Studies on inactivated virus-based vaccines, however, are still scarce. Phase 3 trials of the Sinovac vaccine in Chile and Turkey suggest that inactivated SARS-CoV-2 vaccines effectively prevent COVID-19 and have a good safety profile [15, 16]. More recently, two studies from Chile and Sri Lanka assessed the magnitude of T cell response among Sinovac recipients [17, 18]. Sinovac induced increases in basal lymphocyte subsets including CD3+, CD8+, and CD56+cells. Although vaccination triggered production of antibodies, a decrease in CD19+B lymphocytes was reported. Cellular immune responses were also triggered after vaccination, including increases of T CD4+, T CD8+, and NK cells. Despite these findings, the adaptive immune response induced by inactivated vaccines remains to be clarified and is currently controversial in vaccine development and application. Using suitable adjuvants, inactivated vaccines could also induce cellular immunity [6]. Genetic vaccines such as AZD1222, (viral DNA vector vaccine, UK), BNT162b1 (mRNA vaccine, USA), and mRNA-1273(mRNA vaccine, USA), on the other hand, generate Th1-dominated cellular immune responses [19, 20].

To address this gap in knowledge, it will be particularly significant to clarify the immune changes induced by an inactivated vaccine so that meaningful comparisons of vaccine effectiveness across platforms can be made. At present, induction of Th1-dominated cellular immune responses has been suggested only for the BBV152 vaccine (Bharat Biotech COVAXIN). It was reported that BBV152 vaccine adjuvanted with aluminum hydroxide gel (Algel), or TLR7/8 agonist chemisorbed Algel evoked a Th1-dominated cellular immune response [21]. The Sinopharm and Sinovac vaccines used beta-propiolactone-inactivated aluminum hydroxide adjuvants which specifically induced Th2-dominated cellular immune response [5, 9, 10]. Aluminum hydroxide activates the NLRP3 receptor subunit of the inflammasome and promotes the secretion of high-levels of inflammasome-derived IL-1β and IL-18, thus activating proinflammatory mechanisms of the immune system [22]. Furthermore, aluminum adjuvants enhance the adaptive immune response mediated by Th2 cells and activate the function of B lymphocytes to induce antibody production. The Sinopharm vaccine evoked a Th2-type cell response with decreased IFN-γ and increased IL-5, while the Sinovac vaccine evoked a Th2 type cell response with increases in both IL-5 and IL-8. Changes in specific lymphocyte subsets differed between the two vaccines, with the Sinopharm vaccine showing increases in T and B lymphocyte subsets, and the Sinovac vaccine showing increases in T and NK lymphocyte subsets [23]. The study focused on the Sinopharm vaccine did not detect significant changes in various cytokines (including T helper 2 cell-related cytokines IL-4, IL-5, and IL-10) [24]. Moreover, the Th2-dominated cellular immune response evoked by the Sinopharm vaccine promoted humoral immunity and the production of antibodies. Furthermore, vaccination with Sinopharm also caused a modest cellular immune response.

The observational and longitudinal study from Vályi-Nagy et al. compared the adaptive (humoral and T cell-mediated) immune responses elicited by Sinopharm and BNT162b2 vaccines against SARS-CoV-2 virus among 57 healthy adult Hungarian volunteers [25]. The immune response was also studied in a control group of COVID-19 convalescent individuals for whom time-after infection was not defined. This important study is the first comparative analysis of adaptive immunity to Sinopharm and BNT162b2 shortly after their second dose. Irrespective of the vaccine received, the specific-humoral response against SARS-CoV-2 among all individuals was detectable. However, anti-SARS-CoV-2 antibody levels were significantly higher among individuals vaccinated with two doses of BNT162b2 compared to Sinopharm (99.4% versus 71.0%, respectively). This difference was even higher among individuals with verified prior SARS-CoV-2 infection, reflecting an immune-strengthening effect also known as “hybrid immunity” that refers to immunity arising from infection followed by vaccination. While both platforms resulted in the development of measurable specific anti-spike (RBD, S1/S2) serum IgG responses, anti-spike serum IgA antibodies were detectable for all

BNT162b2 vaccine recipients but only for 70% of the individuals vaccinated with Sinopharm. In contrast, only Sinopharm vaccinees had anti-nucleocapsid IgG antibodies.

Because the phenotype of lymphocyte populations in blood was examined in individuals vaccinated with Sinopharm but not in those who received BNT162b2, comparisons between phenotypes of lymphocyte populations for groups inoculated with these vaccines could not be performed.

Only small differences were found among mRNA (BNT162b2) and inactivated virus (Sinopharm) participants for specific T cell response measured as cumulative number of IFNγ-secreting cells. However, specificity varied: the mRNA vaccine BNT162b2 induced T cell responses that narrowly target the spike protein most susceptible to mutations, whereas the inactivated virus vaccine Sinopharm elicited much broader responses against epitopes of spike, nucleocapsid, and membrane proteins. Because the Sinopharm vaccine targeted many more epitopes as compared with the BNT162b2 vaccine, vaccination with Sinopharm could mitigate the impact of immune escape by new mutations in SARS-CoV-2. Individuals from both groups with prior exposure to SARS-CoV-2 showed a slightly but not uniformly stronger T cell response compared to naïve volunteers. Interestingly, the magnitude and specificity of the T cell response to SARS-CoV-2 structural proteins (S, N, and M) were similar in healthy volunteers and in convalescent patients vaccinated with Sinopharm, while volunteers that received the BNT162b2 produced a stronger T cell response restricted to the spike-derived peptides.

Moreover, higher inter-individual differences in antibody and T cell responses were observed in the BNT162b2 cohort as compared to the Sinopharm cohort. This could be explained by the lower number of immunodominant epitopes in the spike-based vaccine as compared to the inactivated SARS-CoV-2 virus vaccine, where epitopes presented will vary with differences in HLA alleles expressed. The observations reported by Vályi-Nagy et al. are of high interest because they pioneer the comparison of immune responses elicited by nucleic acid-based and inactivated virus-based SARS-CoV-2 vaccines. Future studies using larger sample sizes, longer follow-up periods, and including groups of diverse ages (children, adolescents, older adults) are warranted.

The relative contributions of anti-spike versus anti-nucleocapsid responses in the induction and maintenance of effective anti-SARS-CoV-2 immunity after vaccine challenge are largely unexplored. It is clear that both virus-specific antibodies and T lymphocytes are present in patients who recovered from COVID-19 [26]. In this regard, an estimated half-life of 200 days for a broad-based immune response was found among convalescent individuals, including humoral and cellular polyfunctional virus specific CD4 + and CD8 + T cell responses. The CD4 + T cell response targeted various SARS-CoV-2 proteins comparably, whereas the CD8 + T cell response preferentially targeted the nucleoprotein, highlighting the potential importance of including nucleoprotein sequences as an additional immunogen in future nucleic acid-based vaccines [27]. Notably, anti-nucleocapsid IgG antibodies, or at least a subset of them, have virus-neutralizing activity. Therefore, immune responses targeting the nucleocapsid determinants could be important to broaden epitope coverage and immune effector mechanisms [28].

Several investigators have shown that vaccination of convalescent people can yield neutralizing antibodies with increased potency and breadth which can be up to a thousand-fold higher than those induced by infection or vaccination alone, suggesting that one way of controlling the pandemic may be the induction of a hybrid immunity-like response using a third booster dose [29–32]. The data presented by Vályi-Nagy et al. suggests that the Sinopharm vaccine could elicit a T cell response in naïve individuals that is comparable to that seen in convalescent patients [25]. Hence, administration of two-doses of Sinopharm that would mimic a "wild-type virus" primary infection, followed by a heterologous prime-boost with DNA or mRNA-based vaccines could provide a strategy to increase vaccine effectiveness. The humoral immune responses elicited by this "heterologous vaccination" strategy were recently evaluated in COVID-19-naïve Lebanon individuals. These studies found higher anti-spike IgG geometric mean titers in volunteers that received "heterologous vaccination" as compared to homologous BNT162b2 immunization [33]. Similar studies should be carried out in countries with limited access to mRNA vaccines where large populations have received one or two doses Sinopharm or Sinovac vaccines, in which second or booster doses of mRNA vaccines may be an effective strategy to significantly

increase immunogenicity induced by inactivated virus vaccines alone, thus potentially providing protection both against existing and emerging variants.

Declarations

Conflict of interest The authors declare no competing interests.

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