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Perspective

Role of inactivated SARS-CoV-2 vaccine induced T cell responses in ameliorating COVID-19 severity

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine is one of the most effective weapons to fight the coronavirus disease 2019 (COVID-19) pandemic (Lazarus et al., 2022). Among all SARS-CoV-2 vaccines generated on different platforms, those consisting of the inactivated virus, such as BBIBP-CorV and CoronaVac, have been frequently used (WHO, 2023). By January 30, 2023, 92.9% of the entire, all-ages population had initiated vaccination and 90.6% had completed their primary series based on the whole population size reported in the seventh census of Chinese mainland (China CDC, 2023). However, compared to SARS-CoV-2 mRNA vaccines, which can elicit extremely high quantities of anti-spike (S) antibodies, the levels of neutralizing antibodies induced by inactivated SARS-CoV-2 vaccines are quite lower and wane quickly (Peng et al., 2022; Lim et al., 2021). This raised a great concern regarding whether inactivated vaccines are as effective as mRNA vaccines in preventing SARS-CoV-2 infection. With the emergence of more and more new SARS-CoV-2 variants such as Omicron or its sub-variants, which efficiently escaped the neutralizing ability of antibodies elicited by vaccines based on Wuhan isolates (Kherabi et al., 2022), the virological landscape of the COVID-19 pandemic has profoundly changed (Collie et al., 2022). From the concerns of clinicians, relevant evaluation indicators of COVID-19 vaccines include not only their ability to prevent infection, but also to reduce transmission, disease severity, and sequelae of COVID-19. In this regard, the efficacy of inactivated SARS-CoV-2 vaccines in preventing the development of severe COVID-19 and death after SARS-CoV-2 Omicron BA.2 strain infection has been demonstrated during two local COVID-19 outbreaks in Chinese cities of Hong Kong and Shanghai, respectively. Data from the Shanghai outbreak in the spring of 2022 showed that while the inactivated vaccine was only 16.3% (95% CI: 15.4%–17.2%) effective in preventing SARS-CoV-2 infection, it was 88.6% (95% CI: 85.8%–90.9%) effective against severe disease and 91.7% (95% CI: 86.9%–94.7%) against death from COVID-19. In comparison, the adenovirus type 5-vectored vaccine was 77.9% (95% CI: 15.6%–94.2%) effective against severe COVID-19 (Huang et al., 2022). Similarly, data from the Hong Kong outbreak in early 2022 showed that COVID-19 vaccines offer very high levels of protection against severe or fatal outcomes. Two doses of either vaccine (mRNA- or inactivated-virus-based) can protect against severe COVID-19 as well as COVID-19 death within a positive test in 28 days, with higher effectiveness among adults aged 60 years or older. BNT162b2 showed a higher vaccine effectiveness (89.3%, 95% CI: 86.6%–91.6%) in protecting from infection than CoronaVac (69.9%, 95% CI: 64.4%–74.6%). However, three doses of either vaccine offered very high levels of protection against severe or death outcomes (97.9%, 95% CI: 97.3%–98.4%) (Mcmenamin et al., 2022).

The rapid and continuous emergence of novel SARS-CoV-2 lineages that can escape the neutralization ability of vaccine-induced antibodies has led us to ask a key question: how should we evaluate the immune protective efficacy of SARS-CoV-2 vaccines? An increasing number of studies have revealed that all the currently available vaccines generated from different platforms can efficiently achieve neutralizing immunity against Omicron or its sublineages (Wang et al., 2022; Costa et al., 2022; Deshpande et al., 2022; Pérez-Then et al., 2022; Pajon et al., 2022; Andrews et al., 2022). In this line, it's not recommended by the US Food and Drug Administration (FDA) to test antibody responses for SARS-CoV-2 to determine immunity or protection from COVID-19, especially among vaccinated individuals (FDA, 2021). Besides, in addition to the ability of antibodies to prevent viral infection, T cells perform other necessary immunological functions to limit viral replication by reducing the number of infected cells, thereby reducing COVID-19 severity (Cromer et al., 2021). Indeed, the clinical observations that inactivated SARS-CoV-2 vaccines could effectively prevent the development of severe COVID-19 and death post-infection suggest that T-cell responses, not antibodies, induced by these vaccines are those exerting protective effects. We and others have previously systematically characterized SARS-CoV-2-specific T-cell responses elicited by inactivated vaccines (Li et al., 2021; Costa et al., 2022; Chen et al., 2022). Unlike COVID-19 mRNA vaccines, which express only viral spike (S) protein, inactivated SARS-CoV-2 vaccines contain all the structural viral proteins present in the virions. Therefore, we could detect T-cell responses against not only S but also other diverse structural SARS-CoV-2 proteins, such as membrane (M) and nucleocapsid (N) proteins in vaccinated individuals (Li et al., 2021). These inactivated vaccine-induced SARS-CoV-2-specific

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T-cell immunity is mostly carried out by $CD4^+$ T cells, with $CD8^+$ T cells to a much lesser extent. Longitudinal analysis indicated that inactivated vaccine-induced $CD4^+$ T-cell responses waned quickly following a single vaccine dose, but could be boosted and became more sustained after a second dose (Li et al., 2021).

However, an unaddressed important question was whether inactivated vaccines elicited a comparable magnitude of T-cell response with that of S-mRNA vaccines. Recently, Joey Ming Er Lim et al. performed a comparative analysis of SARS-CoV-2-specific T-cell responses induced by mRNA or inactivated COVID-19 vaccines among healthy populations (Lim et al., 2022). The results showed that inactivated vaccines induced a lower magnitude of S-specific T-cell response than mRNA vaccines. However, compared to the sole S-specific T-cell response induced by mRNA vaccines, inactivated vaccines induced a wider range of heterogenicity of T-cell responses targeting M, N, and other structural proteins of SARS-CoV-2, which compensated for the lower magnitude of T-cell response against spike protein, and made the total T cell response induced by inactivated vaccine quantitatively comparable to that induced by mRNA vaccine (Lim et al., 2022). In addition, it has been shown that the SARS-CoV-2-specific $CD4^+$ T-cell-response seems to be conserved against the prototype strain, as well as different variants of concerns (VOCs) of SARS-CoV-2, due to mutations occurring mainly within the non-$CD4^+$ T-cell epitope regions (Mazzoni et al., 2022). Consistently, Liu et al. showed that individuals who received the adenovirus vector-based vaccine (Ad26.COV2.S) or mRNA-based vaccine (BNT162b2) had robust S-specific $CD8^+$ and $CD4^+$ T-cell responses, which showed extensive cross-reactivity against the Delta and Omicron variants both in central and effector memory cellular subpopulations (Liu et al., 2022). In line with these results, we can speculate that the inactivated vaccines probably could better tolerate new VOCs of SARS-CoV-2 due to the multi-specific T-cell responses against epitopes located in different viral antigens.

Most of the global population is no longer immunologically naive to SARS-CoV-2 because of prior infection and/or vaccination (Krause et al., 2021). Unlike most parts of the world, China quickly controlled the regional outbreaks of COVID-19 with the dynamic zero-COVID policy, which makes the basic immunity against SARS-CoV-2 in most populations of the Chinese mainland was established solely based on the inoculation of inactivated SARS-CoV-2 vaccines before December 2022. With the attenuated pathogenicity of omicron subvariants, the increased popularization rate of vaccination, and the accumulation of prevention and control experience, the National Health Commission of China adjusted and optimized the prevention and control strategies for COVID-19. Following the policy adjustment, a nationwide spread of infection of Omicron variants (mainly BA.5.2 and BF.7) occurred in the Chinese mainland in December 2022 and January 2023. Recently, the Chinese Center for Disease Control and Prevention (CCDC) released the nationwide COVID-19 clinical and surveillance data from December 9, 2022 to January 30, 2023 (China CDC, 2023). The number of COVID-19 cases in hospitals nationwide peaked at 128,000 on January 5, 2023, before decreasing continually to 14,000 on January 30, 2023, representing an 89.3% reduction from the peak. The number of deaths with SARS-CoV-2 in hospitals reached a daily peak of 4273 on January 4, 2022 and continued to decline thereafter, falling back to 434 on January 30, 2021, with an 89.8% reduction from the peak. Although it is hard to precisely calculate the severity and death rates of this nationwide COVID-19 outbreak, this real-world event still obviously indicates the protection efficacy of inactivated COVID-19 vaccines in reducing COVID-19 severity and death, which has been administrated, according to the report, over 3.4 billion does and covered over 92% of all-ages population in China by January 30, 2023. However, further studies are still needed to address important questions, such as: (1) How do breakthrough infections shape inactivated vaccine-induced T-cell responses? (2) How do repeated boost doses of inactivated vaccines influence T-cell responses? (3) How would inactivated and mRNA vaccines perform in the future when facing any new SARS-CoV-2 strains or VOCs?

Footnotes

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