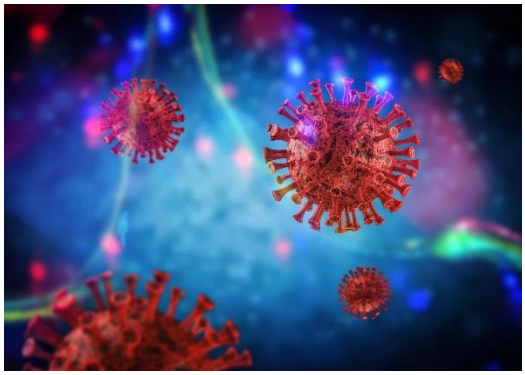
Broad SARS-CoV-2 Variant Protection shown by Intranasal Vaccine

A recent study published determined the efficacy of a codon-deoptimized intranasal live-attenuated vaccine (LAV) against current and future severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants.



Study

Although therapeutic strategies have been developed to treat coronavirus disease 2019 (COVID-19), vaccination remains the most effective way to prevent disease. Currently, available COVID-19 vaccines are typically based on the SARS-CoV-2 spike protein, as its receptor-binding domain (RBD) is targeted by neutralizing antibodies.

Most COVID-19 vaccines have been protective against early SARS-CoV-2 variants of concern; however, this protection decreased sharply as novel variants with mutated RBDs emerged. For example, SARS-CoV-2 Omicron and related variants continue to infect recovered and vaccinated individuals. Moreover, spike mutations reduce the sensitivity to antibody neutralization.

Therefore, it is crucial to develop novel vaccines that both induce broadly neutralizing antibodies and are effective against multiple variants, including those that may emerge in the future. LAVs induce potent and durable immune responses, often with a single dose. The immune response is antigenically broad because LAVs essentially contain the entire virus.

Results

Previously, the current study's researchers developed an infectious clone of wild-type (WT) SARS-CoV-2 assembled from five synthetic DNA fragments. In the current study, the researchers initially used the second and third fragments for CDO and designed 31 constructs, which were not rescuable.

Thus, CDO was restricted to the second fragment, leading to28 constructs. Codons in these constructs were changed to their corresponding low-frequency or rare codons. Sixteen constructs were rescued as infectious viruses and assessed for plaque morphology and replication kinetics.

Two attenuated candidates of CDO-4N-1 and CDO-7N-1 had smaller plaques sizes than WT SARS-CoV-2. Further, Calu-3 and Vero E6 cells infected with CDO-7N-1 and CDO-4N-1 exhibited decreased viral growth kinetics as compared to those infected with the WT virus.

Hamsters infected with CDO-7N-1 and CDO-4N-1 exhibited lower virus titers in bronchoalveolar lavage fluid (BALF) than those infected with the WT virus. Furthermore, the lung pathology of animals infected with CDO-4N-1 was less severe than those infected with WT SARS-CoV-2, whereas little or no pathology was observed in those infected with CDO-7N-1.

CDO-7N-1, which was selected as the lead vaccine candidate, underwent 15 serial passages in Vero E6 cells. Passage 1 (P1), P10, and P15 viruses exhibited the small-plaque phenotype. Moreover, the P15 virus had replication kinetics similar to that of the P1 virus. In addition, the attenuated properties of CDO-7N-1 were sustained after multiple in vivo passages.

Hamsters were subsequently immunized with CDO-7N-1 through the intranasal route, following which sera was collected at various time points. Controls were mock-immunized with phosphate-buffered saline (PBS).

CDO-7N-1 elicited potent neutralizing antibodies, which were maintained for up to 90 days. In fact, specific immunoglobulin G (IgG) responses against different viral proteins were detected in vaccinated animals over protracted periods.

After 28 days, control and vaccinated animals were challenged with WT SARS-CoV-2. Controls exhibited high virus titers in BALF and nose, in addition to prominent lung inflammation with mild/moderate olfactory epithelium atrophy. Comparatively, vaccinated animals did not have any detectable virus in their sera, exhibited no/slight lung inflammation, and maintained normal structure in the nasal turbinate.

K18-hACE2 mice were also immunized with CDO-7N-1 or PBS and challenged with WT SARS-CoV-2 after 21 days. One week after the viral challenge, the brains and lungs of CDO-7N-1 vaccinated mice lacked detectable virus, whereas PBS recipients exhibited high viral replication. The lungs of CDO-7N-1 recipients exhibited significantly lower lung inflammation, as well as reduced expression of both proinflammatory chemokines and cytokines, as compared to PBS recipients.

In another experiment, K18-hACE2 mice were vaccinated with CDO-7N-1 and subsequently challenged with SARS-CoV-2 Beta, Delta, and Omicron variants after 21 days. CDO-7N-1-immunized mice were protected from Beta/Delta infection without experiencing any clinical signs of disease, lung pathology, or detectable virus in the brain, lungs, or nose.

Comparatively, PBS recipients infected with the Beta/Delta variant developed clinical signs of infection, which were accompanied by weight loss and pronounced lung pathology. The Omicron variant is less virulent in K18-hACE2 mice; therefore, no lung pathology or disease signs were detected in CDO-7N-1 recipients or controls.

Virus-specific neutralizing antibodies were identified in CDO-7N-1-vaccinated hamster and K18-hACE2 mouse sera against the D614G strain and Beta, Delta, and Omicron, including XBB.1.5 variants.

Cynomolgus macaques were also vaccinated with CDO-7N-1 or PBS control and monitored for 60 days following immunization before being euthanized. Forty-eight hours after immunization, CDO-7N-1-vaccinated animals exhibited minimal diffuse lymphocytic pulmonary infiltration, whereas one control and one vaccinated macaque did not exhibit any tissue changes.

Blood and clinical parameters were normal for all macaques. Although no pathology was observed in any other organ of controls and vaccinated animals, both vaccinated macaques experienced rhinitis. Antibodies against SARS-CoV-2 were detected at 14- and 40-days following immunization, with increased levels of binding and neutralizing antibodies against the spike and RBD observed in the sera of seven animals.

CDO-7N-1 induced local mucosal immunity, with high levels of spike-specific IgA observed in most macaques. Robust clusters of differentiation 4 (CD4+) and CD8+ T cell responses were also observed in vaccinated animals, with increased production of interferon-γ (IFN-γ).

Conclusion

The CDO-7N-1 vaccine was highly immunogenic, providing robust protection from infection in hamsters and mice and good evidence of immunogenicity in macaques. This intranasal CDO live-attenuated vaccine also elicited high levels of neutralizing antibodies and a potent T-cell response involving CD4+ and CD8+ T-cells with a single immunization.

Overall, the antigenically broad immune response induced by CDO-7N-1 will likely be effective against new variants, requiring mutations in multiple proteins to evade vaccine-induced immunity.

Source:

https://www.news-medical.net/news/20240901/Intranasal-vaccine-shows-broad-SARS-CoV-2-variant-protection.aspx