Received: 18 March 2022 | Revised: 7 April 2022 | Accepted: 27 April 2022

DOI: 10.1111/all.15333

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

NEWS AND VIEWS

A potential immunological silver bullet for COVID-19: The trivalent chimpanzee adenoviral serotype-68 vector (Tri:ChAd)

Humanity has been facing a major challenge recently from a microbe called SARS-CoV-2. Although aged people are more susceptible to COVID-19, the vaccine has been administered even in 5-year-old children so far to control and prevent disease.[1,2] Several strains of SARS-CoV-2 have been reported within two years. Some of these have attracted public attention for their contagiousness, or level of mutations, and are termed variants of concern (VOCs).[3,4] The number of vaccines registered to the World Health Organization in clinical and preclinical development is 144 and 195, respectively.[5] While the generation of different types of vaccines is important for protection effectiveness, the route of vaccine administration is also a key factor. For example, the respiratory mucosal immunity induced by the inhaled aerosol modified vaccinia Ankara Tuberculosis vaccine in humans was not achieved by intradermal injection of the same vaccine.[6]

Providing long-term protection against current and future variants and sustained vaccine-induced herd immunity is a great challenge. Due to the short duration of humoral protection and immunity of the first generation of commercial COVID-19 vaccines, it is imperative to develop a vaccine that provides long-term

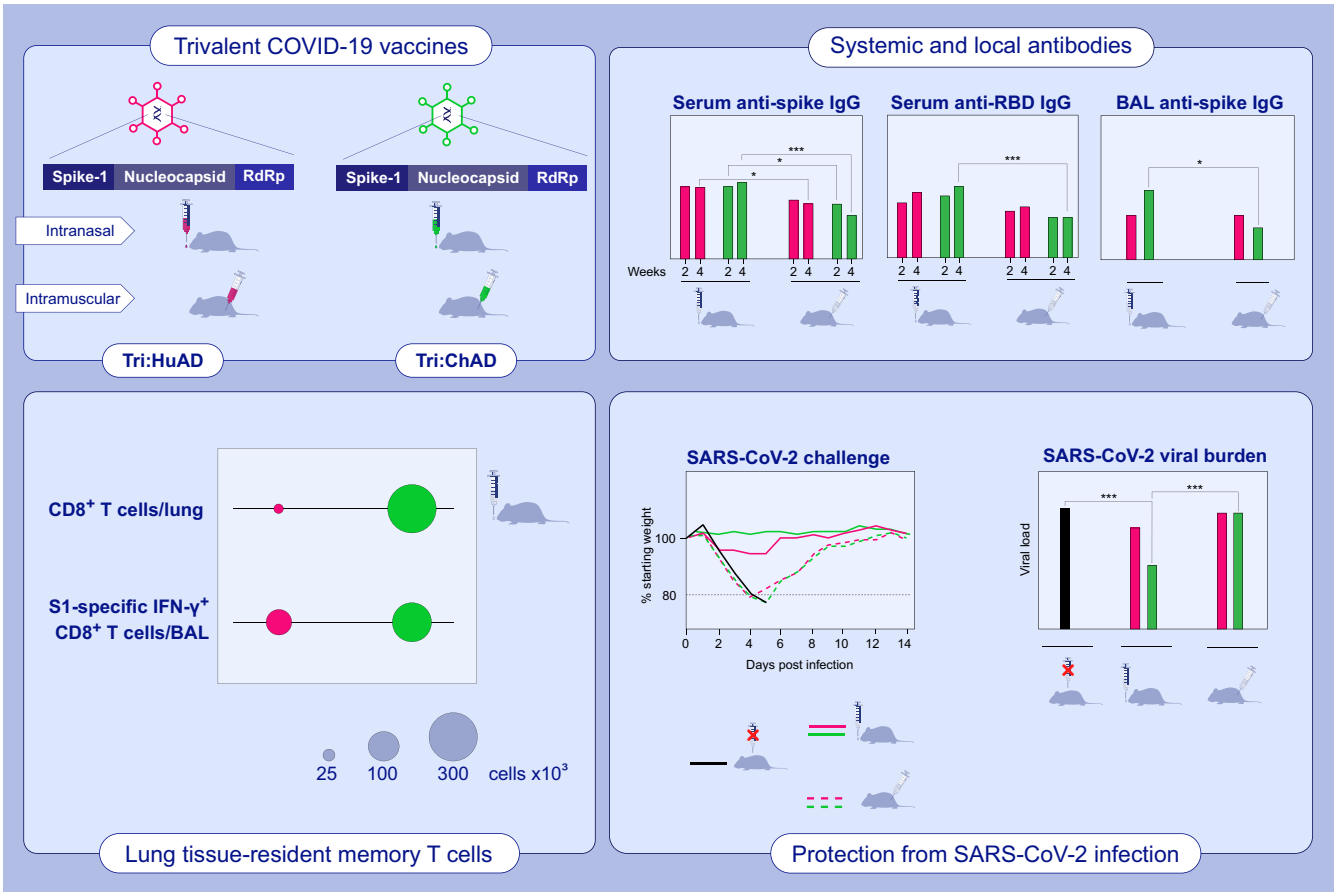

FIGURE 1 Intranasal Tri:ChAd single-dose vaccine is the best vaccine candidate against COVID-19 compared to intramuscular immunization. Intramuscular (i.m.), intranasal (i.n.), trivalent human adenovirus serotype 5 (5×10^7 PFU/Tri:HuAd), trivalent chimpanzee adenovirus serotype 68 (1×10^7 PFU/Tri:ChAd), bronchoalveolar lavage fluid (BAL), interferon-γ (IFN-γ), RNA-dependent RNA polymerase (RdRp)

protection against existing and emerging variants. Janssen Ad26.COV2.S (5×10^{10} viral particles) and Oxford/AstraZeneca ChAdOx1 (5×10^{10} viral particles) are administered as single and two doses, respectively, via intramuscular (i.m.) injection. However, Ad26.COV2.S and ChAdOx1 have generated concern because of some side effects.[7,8] To overcome these problems, Afkhami et al.[9] recently showed that respiratory mucosal delivery of next-generation COVID-19 vaccine provides robust protection against both ancestral and variant strains of SARS-CoV-2.

Afkhami et al.[9] developed adenoviral vectors of trivalent human serotype 5 (5×10^7 PFU/Tri:HuAd) or trivalent chimpanzee serotype 68 (1×10^7 PFU/Tri:ChAd) which are suitable for single-dose intranasal (i.n.) administration in the mouse model (BALB/c, C57BL/6J, B6. Cg-Tg (K18-ACE2) 2Prlmn/J, B cell-deficient mice C. Cg-Igh-J^{tm1Dhu}, BALB/c mice depleted of T cells) and evaluated responses at 2, 4, and 8 weeks post-immunization (Figure 1). Vectors included the full-length S1 domain of spike (S) which contains the N-terminal domain, receptor-binding domain (RBD), and numerous T-cell epitopes. S1 was fused to the vesicular stomatitis virus G protein transmembrane/trimerization domain. This domain was used to provide membrane anchor and facilitation of trimerization and exosomal targeting for enhanced antibody responses. Furthermore, to broaden T-cell immunity against additional viral antigens, nucleocapsid and truncated nsp12 RNA-dependent RNA polymerase proteins were included in vaccine design as a single polyprotein downstream of a porcine teschovirus 2A sequence.

In comparison with i.m. vaccination, i.n. Tri:ChAd vaccine provides significantly greater induced S- and RBD-specific IgG responses in serum and significant amounts of anti-S IgA, superior airway T-cell responses, multifunctional CD8+ T cells with cytotoxic potential within the respiratory tract, multifunctional respiratory mucosal tissue-resident memory T-cell responses, and trained airway macrophages. Concerning memory B cells in systemic lymphoid and local lung tissues, high levels of RBD-specific B cells were formed by i.n. Tri:ChAd compared to i.n. Tri:HuAd. In the lung tissue, only i.n. Tri:ChAd induces these cells. The existence of S1-, N-, and RdRp-specific CD4+ T cells were observed in the airways and spleen following a Tri:ChAd vaccination by i.n. administration but not i.m. I.n. Tri:ChAd vaccine also empowers the Th1-skewed S-specific IgG2a antibody response without Th2 skewing of antibody responses. In addition, i.n. Tri:ChAd vaccine protects against lethal infection by SARS-CoV-2 VOCs which are B.1.1.7 and B.1.351. Surprisingly, the authors found that clinical outcomes/illnesses do not always corroborate with the viral burden. Indeed, while i.n. Tri:ChAd vaccine protected wild-type and B cell- and T cell-deficient mice in clinical outcomes, lack of B or T cells led to partially impaired viral clearance in the lung.

A superior protection against a mouse-adapted SARS-CoV-2 is provided by i.n. immunization rather than i.m. vaccination. Desirable protection of i.n. immunization develops only when humoral and T-cell immunity exist. Vaccine-induced trained innate immunity improves clinical outcomes but it partially controls the viral burden. It is promising to design a vaccine without the vulnerabilities of first-generation vaccines and to develop a cheaper and more attractive vaccine for protection-control in the fight against COVID-19. Thus, this vaccine exhibits extraordinary results for COVID-19 and will be awaited with great interest in primates and clinical phase studies.

KEYWORDS

adenoviral vectors, mucosal immunity, next-generation vaccine, SARS-CoV-2, trained innate immunity

ACKNOWLEDGMENT

We would like to thank Dr. Anna Globinska for assistance in generating the graphical figure.

CONFLICT OF INTEREST

The authors declare that they have no potential conflict of interest.

Ozge Ardicli[1]
Ahmet Kursat Azkur[2]
Dilek Azkur[3]

[1]*Division of Food Processing, Milk and Dairy Products Technology Program, Karacabey Vocational School, University of Bursa Uludag, Bursa, Turkey*
[2]*Department of Virology, Faculty of Veterinary Medicine, University of Kirikkale, Kirikkale, Turkey*
[3]*Division of Pediatric Allergy and Immunology, Department of Pediatrics, Faculty of Medicine, University of Kirikkale, Kirikkale, Turkey*

Correspondence
Ahmet Kursat Azkur, Department of Virology, Faculty of Veterinary Medicine, University of Kirikkale, Kirikkale, Turkey.
Email: azkurkursat@hotmail.com

ORCID

Ozge Ardicli https://orcid.org/0000-0001-6077-0478
Ahmet Kursat Azkur https://orcid.org/0000-0002-5597-8917
Dilek Azkur https://orcid.org/0000-0002-4396-9087

REFERENCES

1. Gerber JS, Offit PA. COVID-19 vaccines for children. *Science*. 2021;374(6570):913.
2. Zhang J-J, Dong X, Cao Y-Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. 2020;75(7):1730-1741.
3. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy*. 2020;75(7):1564-1581.
4. Sariol A, Perlman S. Lessons for COVID-19 immunity from other coronavirus infections. *Immunity*. 2020;53(2):248-263.

5. WHO. COVID-19 vaccine tracker and landscape. Accessed February 22, 2022. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
6. Satti I, Meyer J, Harris SA, et al. Safety and immunogenicity of a candidate tuberculosis vaccine MVA85A delivered by aerosol in BCG-vaccinated healthy adults: a phase 1, double-blind, randomised controlled trial. *Lancet Infect Dis*. 2014;14(10):939-946.
7. Sadoff J, Gray G, Vandebosch AN, et al. Safety and efficacy of single-dose Ad26. COV2. S vaccine against Covid-19. *N Engl J Med*. 2021;384(23):2187-2201.
8. Sokolowska M, Eiwegger T, Ollert M, et al. EAACI statement on the diagnosis, management and prevention of severe allergic reactions to COVID-19 vaccines. *Allergy*. 2021;76(6):1629-1639.
9. Afkhami S, D'Agostino MR, Zhang A, et al. Respiratory mucosal delivery of next-generation COVID-19 vaccine provides robust protection against both ancestral and variant strains of SARS-CoV-2. *Cell*. 2022;185(5):896-915.e19.