CORRESPONDENCE

A SARS-CoV-2 mRNA Vaccine — Preliminary Report

TO THE EDITOR: The positive antibody response to the messenger RNA (mRNA) vaccine described by Jackson et al. (published online on July 14 at NEJM.org)[1] is a hopeful step toward controlling the Covid-19 pandemic. However, this vaccine and other DNA and RNA vaccines against SARS-CoV-2 continuously stimulate cellular production of the target antigen. A mechanism is required to be able to stop the antigen production after a period of time to avoid the possibility of eventual desensitization, as is seen with allergen immunotherapy.[2-5] Without such a mechanism, a sustained lack of response may make SARS-CoV-2 infection a lot worse in the long run. It will be important to evaluate this potential before declaring that any DNA or RNA vaccine is safe and efficacious.

Ronald A. Schachar, M.D., Ph.D.

University of Texas at Arlington
Arlington, TX
ron@2ras.com

Ira H. Schachar, M.D.

Stanford University
Stanford, CA

Dr. R.A. Schachar reports being employed by Pfizer. No other potential conflict of interest relevant to this letter was reported.

This letter was published on August 19, 2020, at NEJM.org.

1. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2 — preliminary report. N Engl J Med. DOI: 10.1056/NEJMoa2022483.
2. Su Y, Romeu-Bonilla E, Anagnostou A, Fitz-Patrick D, Hearl W, Heiland T. Safety and long-term immunological effects of CryJ2-LAMP plasmid vaccine in Japanese red cedar atopic subjects: a phase I study. Hum Vaccin Immunother 2017;13:2804-13.
3. Niezold T, Storcksdieck Genannt Bonsmann M, Maaske A, et al. DNA vaccines encoding DEC205-targeted antigens: immunity or tolerance? Immunology 2015;145:519-33.
4. Scheiblhofer S, Thalhamer J, Weiss R. DNA and mRNA vaccination against allergies. Pediatr Allergy Immunol 2018;29:679-88.
5. Barouch DH, Kunstman J, Glowczwskie J, et al. Viral escape from dominant simian immunodeficiency virus epitope-specific cytotoxic T lymphocytes in DNA-vaccinated rhesus monkeys. J Virol 2003;77:7367-75.

DOI: 10.1056/NEJMc2026616

TO THE EDITOR: Jackson et al. report the successful results of a trial of the mRNA-1273 vaccine, which induced an impressive IgG antibody response. However, Jackson and colleagues, as well as Heaton,[1] in her editorial corresponding to the article, did not comment on IgA. IgA is a crucial first-line defense in mucosal tissues, and we wonder whether there was any increase in SARS-CoV-2–specific IgA.

The role of vaccine-induced IgA is under discussion for parenteral vaccination against rotavirus.[2] Since SARS-CoV-2 primarily infiltrates mucosal tissue, SARS-CoV-2–specific IgA may be necessary for full protection. Moreover, the lack of IgA may cause unprotected spread of SARS-CoV-2 from nasal mucosal tissue. Chumakov and colleagues discussed the use of oral polio vaccine to ameliorate or prevent Covid-19.[3] In both nasal and intestinal cells, Sungnak et al. detected angiotensin-converting enzyme 2 (ACE2), which is crucial for binding of SARS-CoV-2, and transmembrane serine protease 2 (TMPRSS2), which is crucial for uptake of the virus.[4] Thus, the intestinal and nasal mucosa are ideal targets for SARS-CoV-2 and for vaccination to trigger IgA responses. Studies of an oral vaccine containing attenuated SARS-CoV-2 to stimulate an early protective systemic immune response by the highly effective gut-associated immune system are warranted.

Juergen R. Schaefer, M.D.
Yulia Sharkova, M.D.
Tanja Nickolaus, M.D.

University Clinic Marburg
Marburg, Germany
juergen.schaefer@uni-marburg.de

No potential conflict of interest relevant to this letter was reported.

This letter was published on August 19, 2020, at NEJM.org.

1. Heaton PM. The Covid-19 vaccine-development multiverse. N Engl J Med. DOI: 10.1056/NEJMe2025111.
2. Bines JE, Kotloff KL. Next-generation rotavirus vaccines: important progress but work still to be done. Lancet Infect Dis 2020;20:762-4.
3. Chumakov K, Benn CS, Aaby P, Kottilil S, Gallo R. Can existing live vaccines prevent COVID-19? Science 2020;368:1187-8.
4. Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med 2020;26:681-7.

DOI: 10.1056/NEJMc2026616

THE AUTHORS REPLY: We agree with Schachar and Schachar that the interim findings of the phase 1 trial of the mRNA-1273 vaccine against SARS-CoV-2 are promising; these findings provided support for the initiation of the phase 2 and 3 trials that are under way. This vaccine is a lipid nanoparticle–encapsidated, nonreplicating, nucleoside-modified mRNA–based vaccine that, after entering the cell cytoplasm, results in rapid, transient expression of the vaccine antigen.[1] The question regarding the duration of immunity is important, and the phase 1 and 2 trials are designed to follow participants for 1 year after the second vaccination and to obtain samples to characterize humoral and cellular immunologic responses. The phase 3 trial is designed to follow participants for 2 years in order to allow assessment of the durability of protective immunity during that interval.

In reply to Schaefer and colleagues: IgA and IgM responses are exploratory immunologic end points in the phase 1 trial, and reporting of these findings is planned as part of the reporting of the final results. The role of monomeric IgA induced by parenteral vaccines is unknown, and monomeric IgA is unlikely to reach the mucosal compartment in substantial quantities. Mucosal delivery of vaccine would be needed to reliably induce secretory IgA localized in mucosal tissues. In a study of SARS-CoV-2 infection and the use of mRNA-1273 in nonhuman primates, intramuscular administration of the vaccine protected the animals against upper- and lower-airway challenge with SARS-CoV-2, and S-specific IgG and IgA were detected in bronchoalveolar-lavage fluid after the challenge.[2] Although these findings may suggest that antibody responses correlate with protection, as noted by Corbett et al.,[2] further evaluations, including passive-transfer studies and challenge studies of lower, subprotective vaccine doses in nonhuman primates, are warranted to further elucidate antibody specificities or functions that correlate with protection.

Lisa A. Jackson, M.D., M.P.H.

Kaiser Permanente Washington Health Research Institute
Seattle, WA
lisa.a.jackson@kp.org

Paul C. Roberts, Ph.D.
Barney S. Graham, M.D., Ph.D.

National Institute of Allergy and Infectious Diseases
Bethesda, MD

Since publication of their article, the authors report no further potential conflict of interest.

This letter was published on August 19, 2020, at NEJM.org.

1. Bahl K, Senn JJ, Yuzhakov O, et al. Preclinical and clinical demonstration of immunogenicity by mRNA vaccines against H10N8 and H7N9 influenza viruses. Mol Ther 2017;25:1316-27.
2. Corbett KS, Flynn B, Foulds KE, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. N Engl J Med. DOI: 10.1056/NEJMoa2024671.

DOI: 10.1056/NEJMc2026616