

CORRESPONDENCE



Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination

TO THE EDITOR: We recently reported the results of a phase 1 trial of a messenger RNA vaccine, mRNA-1273, to prevent infection with SARS-CoV-2; those interim results covered a period of 57 days after the first vaccination.^{1,2} Here, we describe immunogenicity data 119 days after the first vaccination (90 days after the second vaccination) in 34 healthy adult participants in the same trial who received two injections of vaccine at a dose of 100 μ g. The injections were received 28 days apart. The recipients were stratified according to age (18 to 55 years, 56 to 70 years, or \geq 71 years), and the assays used have been described previously.^{1,2}

At the 100- μ g dose, mRNA-1273 produced high levels of binding and neutralizing antibodies that declined slightly over time, as expected,

but they remained elevated in all participants 3 months after the booster vaccination. Binding antibody responses to the spike receptor-binding domain were assessed by enzyme-linked immunosorbent assay. At the day 119 time point, the geometric mean titer (GMT) was 235,228 (95% confidence interval [CI], 177,236 to 312,195) in participants 18 to 55 years of age, 151,761 (95% CI, 88,571 to 260,033) in those 56 to 70 years of age, and 157,946 (95% CI, 94,345 to 264,420) in those 71 years of age or older (Fig. 1).

Serum neutralizing antibodies continued to be detected in all the participants at day 119. On a pseudovirus neutralization assay, the 50% inhibitory dilution (ID₅₀) GMT was 182 (95% CI, 112 to 296) in participants who were between the ages of 18 and 55 years, 167 (95% CI, 88 to 318) in those between the ages of 56 and 70 years, and 109 (95% CI, 68 to 175) in those 71 years of age or older. On the live-virus focus reduction neutralization test mNeonGreen assay, the ID₅₀ GMT was 775 (95% CI, 560 to 1071), 685 (95% CI, 436 to 1077), and 552 (95% CI, 321 to 947) in the same three groups, respectively. On the live-virus plaque-reduction neutralization testing assay, the 80% inhibitory dilution GMT was similarly elevated at 430 (95% CI, 277 to 667), 269 (95% CI, 134 to 542), and 165 (95% CI, 82 to 332) in the same three groups, respectively (Fig. 1).

At day 119, the binding and neutralizing GMTs exceeded the median GMTs in a panel of 41 controls who were convalescing from Covid-19, with a median of 34 days since diagnosis (range, 23 to 54).² No serious adverse events were noted in the trial, no prespecified trial-halting rules were met, and no new adverse events that were considered by the investigators to be related to the vaccine occurred after day 57.

Although correlates of protection against SARS-CoV-2 infection in humans are not yet

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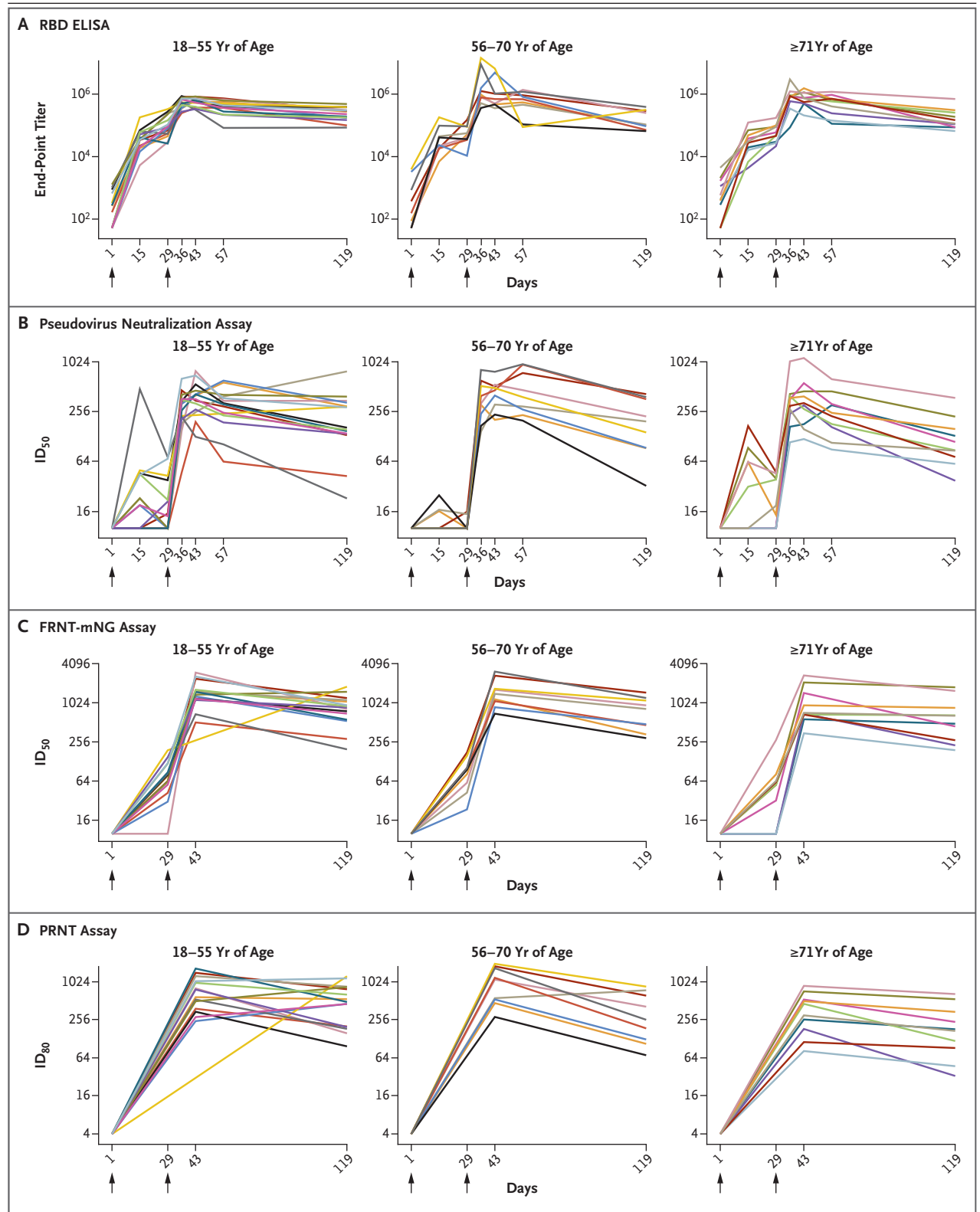


Figure 1 (previous page). Time Course of SARS-CoV-2 Antibody Binding and Neutralization Responses after mRNA-1273 Vaccination.

Shown are data from 34 participants who were stratified according to age: 18 to 55 years of age (15 participants), 56 to 70 years of age (9 participants), and 71 years of age or older (10 participants). All the participants received 100 μg of mRNA-1273 on days 1 and 29, indicated by arrows. The titers shown are the binding to spike receptor-binding domain (RBD) protein (the end-point dilution titer) assessed on enzyme-linked immunosorbent assay (ELISA) on days 1, 15, 29, 36, 43, 57, and 119 (Panel A); the 50% inhibitory dilution (ID_{50}) titer on pseudovirus neutralization assay on days 1, 15, 29, 36, 43, 57, and 119 (Panel B); the ID_{50} titer on focus reduction neutralization test mNeonGreen (FRNT-mNG) assay on days 1, 29, 43, and 119 (Panel C); and the 80% inhibitory dilution (ID_{80}) titer on plaque-reduction neutralization testing (PRNT) assay on days 1, 43, and 119 (Panel D). Data for days 43 and 57 are missing for 1 participant in the 18-to-55-year stratum for whom samples were not obtained at those time points. Each line represents a single participant over time.

established, these results show that despite a slight expected decline in titers of binding and neutralizing antibodies, mRNA-1273 has the potential to provide durable humoral immunity. Natural infection produces variable antibody longevity^{3,4} and may induce robust memory B-cell responses despite low plasma neutralizing activity.^{4,5} Although the memory cellular response to mRNA-1273 is not yet defined, this vaccine elicited primary CD4 type 1 helper T responses 43 days after the first vaccination,² and studies of vaccine-induced B cells are ongoing. Longitudinal vaccine responses are critically important, and a follow-up analysis to assess safety and immunogenicity in the participants for a period of 13 months is ongoing. Our findings provide support for the use of a 100- μg dose of mRNA-1273 in an ongoing phase 3 trial, which has recently shown a 94.5% efficacy rate in an interim analysis.

Alicia T. Widge, M.D.

National Institute of Allergy and Infectious Diseases (NIAID)
Bethesda, MD
alicia.widge@nih.gov

Nadine G. Rouphael, M.D.

Emory University School of Medicine
Decatur, GA

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

Kaiser Permanente Washington Health Research Institute
Seattle, WA

Evan J. Anderson, M.D.

Emory University School of Medicine
Decatur, GA

Paul C. Roberts, Ph.D.

Mamodikoe Makhene, M.D., M.P.H.

NIAID
Bethesda, MD

James D. Chappell, M.D., Ph.D.

Mark R. Denison, M.D.

Laura J. Stevens, M.S.

Andrea J. Pruijssers, Ph.D.

Vanderbilt University Medical Center
Nashville, TN

Adrian B. McDermott, Ph.D.

Britta Flach, Ph.D.

Bob C. Lin, B.S.

Nicole A. Doria-Rose, Ph.D.

Sijy O'Dell, M.S.

Stephen D. Schmidt, B.S.

NIAID
Bethesda, MD

Kathleen M. Neuzil, M.D.

University of Maryland School of Medicine
Baltimore, MD

Hamilton Bennett, M.Sc.

Brett Leav, M.D.

Moderna
Cambridge, MA

Mat Makowski, Ph.D.

Jim Albert, M.S.

Kaitlyn Cross, M.S.

Emmes Company
Rockville, MD

Venkata-Viswanadh Edara, Ph.D.

Katharine Floyd, B.S.

Mehul S. Suthar, Ph.D.

Emory University School of Medicine
Decatur, GA

Wendy Buchanan, B.S.N., M.S.

Catherine J. Luke, Ph.D.

Julie E. Ledgerwood, D.O.

John R. Mascola, M.D.

Barney S. Graham, M.D.

John H. Beigel, M.D.

NIAID
Bethesda, MD

for the mRNA-1273 Study Group*

*The mRNA-1273 Study Group members are listed in the Supplementary Appendix, available with the full text of this letter at NEJM.org.

Drs. Graham and Beigel contributed equally to this letter.

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Trial of Upadacitinib or Abatacept in Rheumatoid Arthritis

TO THE EDITOR: We believe that the trial conducted by Rubbert-Roth et al. (Oct. 15 issue)¹ may not show that upadacitinib was more efficacious than abatacept in patients with rheumatoid arthritis. Janus kinase (JAK) inhibitors such as upadacitinib target interleukin-6 signaling and thereby reduce the level of C-reactive protein (CRP), a dominant constituent of the primary end point of the trial — the composite Disease Activity Score for 28 joints based on the C-reactive protein level (DAS28-CRP; range, 0 to 9.4, with higher scores indicating more disease activity). Consequently, the DAS28-CRP decreased dramatically only in patients who were receiving upadacitinib. Among non-CRP-related outcomes, upadacitinib was not clearly better than abatacept. The reductions in the counts of tender and swollen joints in the two groups were almost identical, and although the patients' global assessment of disease activity improved more with upadacitinib than with abatacept at 12 weeks, no differences were present thereafter.

We do not endorse a DAS28-CRP of less than 2.6 as a threshold for remission. We led the joint American College of Rheumatology–European League against Rheumatism task force that rejected the use of the DAS28-CRP for defining remission.² Because the swollen-joint count is underweighted in the calculation of the DAS28-CRP, patients with a DAS28-CRP of less than 2.6 can have 10 or more swollen joints, a level that is inconsistent with remission.³ Furthermore,

many patients with a DAS28-CRP of less than 2.6 have progressive disease as assessed radiographically. Given the focus on a CRP-dependent end point and the selection of a nonstringent definition of remission, we conclude that this trial did not show clinically meaningful differences between upadacitinib and abatacept.

David Felson, M.D., M.P.H.

Boston University School of Medicine
Boston, MA
dfelson@bu.edu

Josef S. Smolen, M.D.

Medical University of Vienna
Vienna, Austria

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