CORRESPONDENCE

Durable Humoral and Cellular Immune Responses 8 Months after Ad26.COV2.S Vaccination

TO THE EDITOR: Interim immunogenicity and efficacy data for the Ad26.COV2.S vaccine (Johnson & Johnson–Janssen) against coronavirus disease 2019 (Covid-19) have recently been reported.[1-3] We describe here the 8-month durability of humoral and cellular immune responses in 20 participants who received the Ad26.COV2.S vaccine in one or two doses (either 5×10^{10} viral particles or 10^{11} viral particles) and in 5 participants who received placebo.[2] We evaluated antibody and T-cell responses on day 239, which was 8 months after the single-shot vaccine regimen (in 10 participants) or 6 months after the two-shot vaccine regimen (in 10 participants), although the present study was not powered to compare the two regimens.[3] We also report neutralizing antibody responses against the parental WA1/2020 strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as well as against the SARS-CoV-2 variants D614G, B.1.1.7 (alpha), B.1.617.1 (kappa), B.1.617.2 (delta), P.1 (gamma), B.1.429 (epsilon), and B.1.351 (beta).

Antibody responses were detected in all vaccine recipients on day 239 (Fig. 1A, upper panels). The median binding antibody titer against the WA1/2020 receptor-binding domain was 645 on day 29, 1772 on day 57, 1962 on day 71, and 1306 on day 239. The median WA1/2020 pseudovirus neutralizing antibody titer was 272 on day 29, 169 on day 57, 340 on day 71, and 192 on day 239; titers were similar when the analyses were restricted to participants who had received the single-shot vaccine regimen (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Three vaccine recipients had a sharp increase in antibody responses during this time period: 1 recipient had breakthrough SARS-CoV-2 infection that was minimally symptomatic, and 2 received a messenger RNA (mRNA) vaccine. After the exclusion of these 3 participants, antibody responses were relatively stable during the 8-month period, with a reduction in the median neutralizing antibody titer by a factor of 1.8 between peak response on day 71 and the time point for assessing durability on day 239.

On day 29, the median neutralizing antibody titer against the B.1.351 variant was lower by a factor of 13 than the response against the parental WA1/2020 strain; however, by day 239, that factor difference had decreased to 3 (Fig. 1B). After the exclusion of the above-mentioned 3 participants, vaccine recipients who received the single-shot regimen had a median neutralizing antibody titer of 184 against the parental WA1/2020 strain, 158 against the D614G variant, 147 against the B.1.1.7 variant, 171 against the B.1.617.1 variant, 107 against the B.1.617.2 variant, 129 against the P.1 variant, 87 against the B.1.429 variant, and 62 against the B.1.351 variant on day 239 (Fig. 1C and Table S1). These data suggested an expansion of neutralizing antibody breadth associated with improved coverage of SARS-CoV-2 variants over time, including increased neutralizing antibody titers against these variants of concern.

Spike-specific interferon-γ CD8+ and CD4+ T-cell responses were evaluated by intracellular cytokine staining assays and also showed durability and stability over this time period (Fig. 1A, lower panels). The median CD8+ T-cell response was 0.0545% on day 57, 0.0554% on day 85, and 0.0734% on day 239; the median CD4+ T-cell responses were 0.0435%, 0.0322%, and 0.0176%, respectively.

These data show that the Ad26.COV2.S vaccine elicited durable humoral and cellular immune responses with minimal decreases for at least 8 months after immunization. In addition, we observed an expansion of neutralizing antibody breadth against SARS-CoV-2 variants over this time period, including against the more transmissible B.1.617.2 variant and the partially neutralization-resistant B.1.351 and P.1 variants,

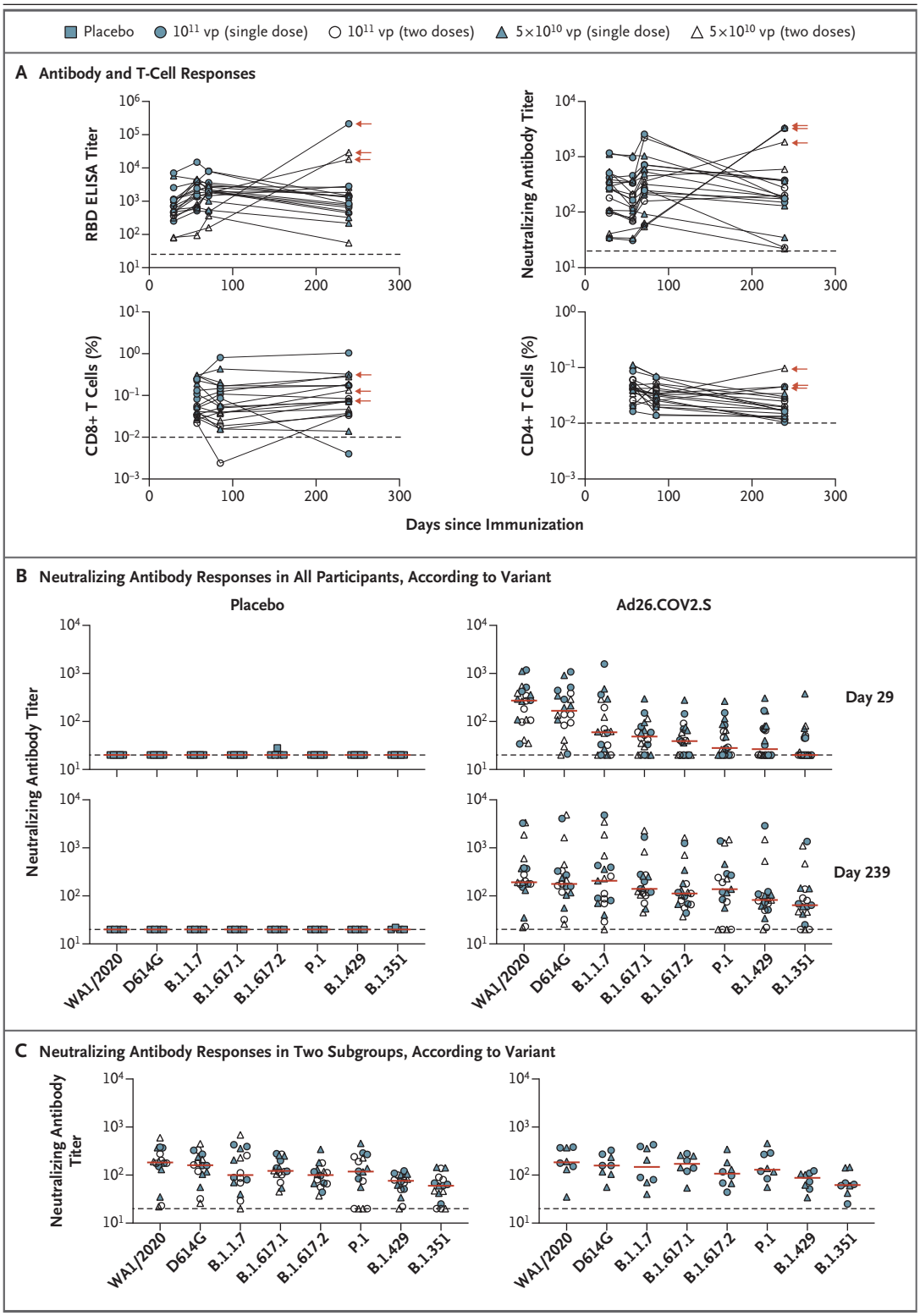
Placebo
10^11 vp (single dose)
10^11 vp (two doses)
5×10^10 vp (single dose)
5×10^10 vp (two doses)
A Antibody and T-Cell Responses
RBD ELISA Titer
Neutralizing Antibody Titer
CD8+ T Cells (%)
CD4+ T Cells (%)
Days since Immunization
B Neutralizing Antibody Responses in All Participants, According to Variant
Placebo
Ad26.COV2.S
Neutralizing Antibody Titer
Day 29
Day 239
WA1/2020
D614G
B.1.1.7
B.1.617.1
B.1.617.2
P.1
B.1.429
B.1.351
C Neutralizing Antibody Responses in Two Subgroups, According to Variant
Neutralizing Antibody Titer

Figure 1 (facing page). Humoral and Cellular Immune Responses after Ad26.COV2.S Vaccination.
Panel A shows binding antibody titers against the receptor-binding domain (RBD) of the parental WA1/2020 strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by enzyme-linked immunosorbent assays (ELISA), pseudovirus neutralizing antibody assays, and intracellular cytokine staining assays showing spike-specific CD8+ and CD4+ T-cell responses on days 29, 57, 71 or 85, and 239. Participants received the Ad26.COV2.S vaccine in one or two doses of either 10^{11} viral particles (vp) or 5×10^{10} vp. Red arrows indicate one vaccine recipient who had breakthrough SARS-CoV-2 infection (who had received a single dose of 10^{11} vp) and two recipients who had also received a messenger RNA vaccine (who had received two doses of 5×10^{10} vp) between days 71 and 239. The horizontal dashed line indicates the lower limit of quantitation. Panel B shows pseudovirus neutralizing antibody titers against the parental WA1/2020 strain as well as the SARS-CoV-2 variants D614G, B.1.1.7 (alpha), B.1.617.1 (kappa), B.1.617.2 (delta), P.1 (gamma), B.1.429 (epsilon), and B.1.351 (beta) on days 29 and 239. Panel C shows pseudovirus neutralizing antibody titers on day 239 following Ad26.COV2.S vaccination after the exclusion of the three above-mentioned participants (at left) and after restriction of the analysis to participants who received a single dose of the Ad26.COV2.S vaccine (at right). In Panels B and C, the horizontal red bar indicates the median response. For the two-dose vaccine, immunizations were administered on days 1 and 57.

which suggests maturation of B-cell responses even without further boosting. The durability of immune responses elicited by the Ad26.COV2.S vaccine was consistent with the durability recently reported for an Ad26-based Zika vaccine.[4] Longitudinal antibody responses to mRNA Covid-19 vaccines have also been reported for 6 months but with different kinetics of decreasing titers.[5] The durability of humoral and cellular immune responses 8 months after Ad26.COV2.S vaccination with increased neutralizing antibody responses to SARS-CoV-2 variants over time, including after single-shot vaccination, further supports the use of the Ad26.COV2.S vaccine to combat the global Covid-19 pandemic.

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Requests for access to the study data can be submitted to Dr. Barouch at dbarouch@bidmc.harvard.edu.

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1. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med 2021;384:2187-201.
2. Stephenson KE, Le Gars M, Sadoff J, et al. Immunogenicity of the Ad26.COV2.S vaccine for COVID-19. JAMA 2021;325:1535-44.
3. Sadoff J, Le Gars M, Shukarev G, et al. Interim results of a phase 1–2a trial of Ad26.COV2.S Covid-19 vaccine. N Engl J Med 2021;384:1824-35.
4. Salisch NC, Stephenson KE, Williams K, et al. A double-blind, randomized, placebo-controlled phase 1 study of Ad26.ZIKV.001, an Ad26-vectored anti-Zika virus vaccine. Ann Intern Med 2021;174:585-94.
5. Doria-Rose N, Suthar MS, Makowski M, et al. Antibody persistence through 6 months after the second dose of mRNA-1273 vaccine for Covid-19. N Engl J Med 2021;384:2259-61.

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