A bivalent SARS-CoV-2 monoclonal antibody combination does not affect the immunogenicity of a vector-based COVID-19 vaccine in macaques

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Human monoclonal antibodies (mAbs) that target the spike glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) offer a promising approach for the prevention and treatment of coronavirus disease 2019 (COVID-19). Suboptimal global vaccination rates, waning immunity in vaccinated individuals, and the emergence of SARS-CoV-2 variants of concern, the use of mAbs for COVID-19 prevention may increase and may need to be administered together with vaccines in certain settings. However, it is unknown whether administration of mAbs will affect the immunogenicity of SARS-CoV-2 vaccines. Using an adenovirus vector-based SARS-CoV-2 vaccine, we show that simultaneous administration of the vaccine with SARS-CoV-2 mAbs does not diminish vaccine-induced humoral or cellular immunity in cynomolgus macaques. These results suggest that SARS-CoV-2 mAbs and viral vector-based SARS-CoV-2 vaccines can be administered together without loss of potency of either product. Additional studies will be required to evaluate coadministration of mAbs with other vaccine platforms.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), identified in 2019 (1), is the etiologic agent of coronavirus disease 2019 (COVID-19). SARS-CoV-2 has led to more than 530 million infections and more than 6.3 million deaths worldwide (2). Since the isolation and identification of SARS-CoV-2, several effective vaccines targeting the viral surface spike (S) glycoprotein were developed (3, 4). However, global vaccine distribution challenges, waning durability over time in vaccinated individuals, and the emergence of virus variants of concern has led to the need to develop additional interventions as complementary tools to vaccines.

The development of monoclonal antibodies (mAbs) that neutralize SARS-CoV-2 offers one such promising approach for COVID-19 prevention and treatment. These mAbs may have an increased role in the evolving pandemic, and they may need to be administered in conjunction with vaccines in outbreak settings. Several mAbs that focus on the receptor binding domain (RBD) of SARS-CoV-2 S protein have shown benefit in both preclinical (5, 6) and clinical settings (7). However, an important question is whether coadministration of mAbs with vaccines will reduce vaccine immunogenicity.

Using a nonhuman primate (NHP) model, we sought to address this gap in knowledge by investigating whether mAbs affect the immunogenicity of a prototypic viral vector–based SARS-CoV-2 vaccine. We evaluated the effect of coadministering the previously described SARS-CoV-2 human mAb cocktail AZD7442 consisting of tixagevimab (AZD8895) and cilgavimab (AZD1061) (6, 8) on the immunogenicity of a vector-based rhesus adenovirus serotype 52 (RhAd52) vaccine expressing SARS-CoV-2 S protein with two proline stabilizing mutations (RhAd52-S.PP) (9).

RESULTS

AZD7442 mAb combination shows a biphasic pharmacokinetic profile when coadministered with a SARS-CoV-2 viral-vector vaccine

Twenty-four cynomolgus macaques (n = 6 per group) were immunized with RhAd52 expressing WA1/2020 SARS-CoV-2 S protein with two proline stabilizing mutations (RhAd52-S.PP) (9) by the intramuscular route. Groups received concurrent administration of AZD7442 mAbs (4, 0.5, or 0 mg/kg) or isotype-matched sham mAb R347 (4 mg/kg) by the intravenous route. Antibody pharmacokinetics were assessed by a human immunoglobulin G (IgG)–specific enzyme-linked immunosorbent assay (ELISA) (5) and showed typical biphasic profiles of rapid serum distribution followed by slower elimination phases (Fig. 1 and table S1). Peak mAb titer were generally observed on day 3 after administration and were dose dependent. Animals administered AZD7442 (4 mg/kg) exhibited a median peak concentration of 58.6 μg/ml (range of 43.5 to 85.1 μg/ml). Animals administered AZD7442 (0.5 mg/kg) exhibited a median peak of 5.8 μg/ml (range of 4.2 to 15.6 μg/ml), with all animals having undetectable mAb titers at study conclusion. Animals receiving IgG isotype control antibody R347 at 4 mg/kg had a median peak of 63.4 μg/ml (range of 55.5 to 83.9 μg/ml) and detectable mAb titers throughout the study duration. Human IgG was not detected in the group that received RhAd52-S.PP (9) without mAb coadministration (Fig. 1 and table S1).

AZD7442 mAb combination exhibits varying neutralization activity against SARS-CoV-2 parental and Omicron pseudo-viruses

To evaluate the functional activity of the SARS-CoV-2–specific AZD7442 mAb cocktail in vivo, a lentivirus-based pseudo-virus neutralization assay (10) against the matching SARS-CoV-2
WA1/2020 virus strain was performed. Experimental groups receiving AZD7442 at either 4 or 0.5 mg/kg exhibited median peak half-maximal neutralizing titers (NT$_{50}$) that were higher than those observed in the R347 (4 mg/kg) or RhAd52-S.PP alone control groups (Fig. 2A and table S2). Peak NT$_{50}$ titers were dose dependent, concordant with the pharmacokinetic data. The ZD7442 group (4 mg/kg) exhibited a median peak titer of 4.1 log$_{10}$ NT$_{50}$ (range of 3.9 to 4.5), the ZD7742 group (0.5 mg/kg) showed a median peak titer of 3.3 log$_{10}$ NT$_{50}$ (range of 2.9 to 3.9), the R347 control group (4 mg/kg) demonstrated a median peak titer of 2.4 log$_{10}$ NT$_{50}$ (range of 1.7 to 3.1), and the RhAd52-S.PP alone group showed a median peak titer of 2.6 log$_{10}$ NT$_{50}$ (range of 2.0 to 3.5). The latter two groups that received RhAd52-S.PP either alone or with R347 showed comparable NT$_{50}$ profiles, reflective of vaccine-induced neutralizing antibodies (Fig. 2A and table S2). The pseudo-virus neutralization assay was unable to distinguish between the AZD7442 mAbs and endogenous vaccine-induced neutralizing antibodies.

We also compared NT$_{50}$ titers against the B.1.1.529 (Omicron) variant on day 7. In this analysis, the AZD7442 mAb cocktail showed low but detectable NT$_{50}$ titers to B.1.1.529 (Fig. 2B and table S3). The Omicron NT$_{50}$ titers from the two groups that received the AZD7442 cocktail were higher than the control groups (adjusted $P < 0.0005$, $P < 0.005$; Fig. 2B and table S3). These data show that AZD7442 retains partial neutralization activity against the Omicron variant.

Viral-vectored SARS-CoV-2 vaccine–induced humoral immunity is not affected by the coadministration of the AZD7442 mAb cocktail

To quantify vaccine-induced antibodies and to differentiate them from the infused AZD7442 mAbs, a SARS-CoV-2 WA1/2020 RBD endpoint binding ELISA assay using a secondary anti-macaque IgG antibody that did not cross-react with human IgG was used. Negligible antibody titers were observed at baseline (Fig. 3A and table S4). Macaque RBD-specific binding antibody titers were first observed in all four experimental groups at 2 weeks after vaccination. At peak immunogenicity (day 28), comparable macaque RBD-specific binding antibody responses were observed across all groups with no significant ($P > 0.05$) differences between the groups (Fig. 3B and table S4). These antibodies remained stable through the study conclusion at week 36 (Fig. 3A and table S4). These antibody titers represent vaccine-induced binding antibodies and not the human mAbs in AZD7442, showing that the AZD7442 mAb cocktail did not affect the humoral immunogenicity of the RhAd52-S.PP vaccine.

Vaccine-induced humoral immunity against SARS-CoV-2 variants is unaffected by the presence of the AZD7442 mAb cocktail

To assess whether AZD7442 affected vaccine-induced humoral immunity against multiple SARS-CoV-2 variant lineages, multiplex
Fig. 2. SARS-CoV-2 pseudo-virus neutralization titers are detectable after co-administration of AZD7442 mAb with a SARS-CoV-2 viral-vectored vaccine. 

(A) WA1/2020 NT50 neutralization titers were determined by a SARS-CoV-2 lentiviral pseudo-virus neutralization assay. Each line corresponds to a single animal, and the red line depicts the median (n = 6 per group). 

(B) B.1.1.529. NT50 neutralization titers were determined by a SARS-CoV-2 lentiviral pseudo-virus neutralization assay. Red horizontal bars indicate median values. A single animal was excluded from the RhAd52-S-PP + AZD7442 (4 mg/kg), RhAd52-S-PP + AZD7442 (0.5 mg/kg), and RhAd52-S-PP groups because of the high assay background observed with baseline samples. Each data point is represented by a single technical replicate. Data were generated over several batch analyses of samples (N = 1 experiment). One-way ANOVA with Tukey correction was used for statistical analyses. ****P_{adj} < 0.0005 and *P_{adj} < 0.05.

IgG serology assays [Meso Scale Diagnostics (MSD)] against panels of S protein or RBD variant antigens were performed at peak immunogenicity (day 28). For this analysis, the same anti-macaque IgG detection antibody used in the endpoint ELISA that did not cross-react to human IgG was used. A comparison of the vaccine-induced S protein and RBD IgG binding responses against parental WA1/2020 and current, prominent circulating strains B.1.617.2 and B.1.1.529 revealed no notable differences between groups receiving the RhAd52-S-PP vaccine either in the presence or absence of AZD7442 (P > 0.05) (Fig. 4 and tables S5 and S6). Binding antibody responses were also not different at peak immunogenicity against B.1.351, B.1.1.7, and P.1 S protein and RBD variant antigens (fig. S1 and tables S5 and S6). These data were concordant with the ELISA data (Fig. 3B and table S4). These data show that vaccine-induced humoral immunity against multiple SARS-CoV-2 variants was not affected by coadministration of the AZD7442 mAb cocktail with the vaccine.

AZD7442 mAb cocktail does not affect vaccine-induced interferon-γ cellular immunity

The potential impact of the AZD7442 mAbs on vaccine-elicted CD8+ and CD4+ cellular immune responses was assessed by interferon-γ (IFN-γ) intracellular cytokine staining assays at week 10 using overlapping S peptides from the WA1/2020 strain. Comparable S protein–specific CD4+ and CD8+ T cell responses were observed in all groups receiving the vaccine, regardless of coadministration of the AZD7442 mAbs (P > 0.05) (Fig. 5 and table S7). These data show that vaccine-elicted IFN-γ-mediated cellular immunity was not affected by the coadministration of the AZD7442 mAb cocktail with the vaccine.

There is no direct interaction between AZD7442 mAb combination and RhAd52-S-PP vaccine

Last, to assess whether there was any direct binding between the AZD7442 mAbs and the RhAd52-S-PP vaccine, surface plasmon resonance assays were performed. A titration series of AZD7442 flowed over immobilized RhAd52-S-PP showed no observable binding (Fig. 6 and table S8). These data indicate that there was no notable interaction between AZD7442 mAb cocktail and the RhAd52-S-PP vaccine.

DISCUSSION

Multiple vaccines and mAbs have been developed for the prevention of SARS-CoV-2 infection and development of COVID-19. It is likely that vaccines and mAbs may need to be used simultaneously in certain outbreak settings, and thus, it is important to determine whether one intervention may affect the other. In the current study, we demonstrate that administration of a bivalent combination of SARS-CoV-2 mAbs (5, 6, 8) with a prototypic viral-vectored vaccine (9) did not lead to reduced potency of either intervention. Specifically, the SARS-CoV-2 mAbs did not diminish the kinetics, durability, or breadth of vaccine-induced humoral and cellular immunity.

The AZD7442 mAb cocktail retained some neutralization activity against the SARS-CoV-2 B.1.1.529 (Omicron) variant. This finding is in line with emerging data that show that many SARS-CoV-2 S protein–mediated cellular immunity was not affected by the AZD7442 mAb cocktail with the vaccine.

This study has several important limitations. First, the generalizability of our data to other vaccine platforms, including mRNA vaccines and adjuvanted protein vaccines, remains to be determined. It is possible that mAbs may affect protein-based vaccines more than gene-based vaccines. Second, although these current data show that SARS-CoV-2 mAbs can be coadministered with a vector-based vaccine without loss of potency of either product, further studies would need to assess any potential impact on protective efficacy.
important differences exist between macaques and humans, and thus, clinical trials will be required to confirm these results. Nevertheless, the current data demonstrate that SARS-CoV-2 mAbs and an adenovirus vector–based vaccine can be coadministered in macaques.

**MATERIALS AND METHODS**

**Study design**

This study was designed to assess the impact of potent neutralizing SARS-CoV-2 mAbs on the immunogenicity of a genetic-based, prototypic viral vector–based SARS-CoV-2 vaccine when they are coadministered and was powered to show a twofold difference in the current data demonstrate that SARS-CoV-2 mAbs and an adenovirus vector–based vaccine can be coadministered in macaques.

**Human IgG mAb ELISA**

Animals were assessed over a 36-week period for human IgG mAb pharmacokinetics in serum using a previously described method (5). Briefly, ELISA plates were coated overnight at 4°C with goat anti-human IgG (H + L) secondary antibody (monkey preadsorbed) (1 μg/ml; Novus Biologicals) and then blocked for 2 hours. The serum samples were assayed at threefold dilutions starting at a 1:3 dilution in Blocker Casein in phosphate-buffered saline (PBS) (Thermo Fisher Scientific) diluent. Samples were incubated for 1 hour at ambient temperature and then removed, and plates were washed. Wells then were incubated for 1 hour with horseradish peroxidase (HRP)–conjugated goat anti-human IgG (monkey preadsorbed) (Southern Biotech) at a 1:4000 dilution. Wells were washed and then incubated with the SureBlue Reserve tetramethylbenzidine (TMB) Microwell Peroxidase Substrate (SeraCare) (100 μl per well) for 3 min, followed by the TMB Stop Solution (SeraCare) to stop the reaction (100 μl per well). Microplates were read at 450 nm. The concentrations of the human mAbs were interpolated from the linear range of concurrently run purified human IgG (Sigma-Aldrich) standard curves using Prism software, version 8.0 (GraphPad).

**Pseudo-virus neutralizing antibody assay**

The SARS-CoV-2 pseudo-viruses expressing a luciferase reporter gene were used to measure pseudo-virus neutralizing antibodies (10). Briefly, the packaging construct pS Pax2 (AIDS Resource and Reagent Program), luciferase reporter plasmid pLenti-CMV Puro-Luc (Addgene), and S protein expressing pDNA3.1-SARS-CoV-2 SACT were cotransfected into human embryonic kidney (HEK) 293T cells (American Type Culture Collection, CRL_3216) with 10 11 viral particles of viral antigens by multiplex electrochemiluminescence serum using a previously described method (5). Briefly, ELISA plates were coated overnight at 4°C with goat anti-human IgG (H + L) secondary antibody (monkey preadsorbed) (1 μg/ml; Novus Biologicals) and then blocked for 2 hours. The serum samples were assayed at threefold dilutions starting at a 1:3 dilution in Blocker Casein in phosphate-buffered saline (PBS) (Thermo Fisher Scientific) diluent. Samples were incubated for 1 hour at ambient temperature and then removed, and plates were washed. Wells then were incubated for 1 hour with horseradish peroxidase (HRP)–conjugated goat anti-human IgG (monkey preadsorbed) (Southern Biotech) at a 1:4000 dilution. Wells were washed and then incubated with the SureBlue Reserve tetramethylbenzidine (TMB) Microwell Peroxidase Substrate (SeraCare) (100 μl per well) for 3 min, followed by the TMB Stop Solution (SeraCare) to stop the reaction (100 μl per well). Microplates were read at 450 nm. The concentrations of the human mAbs were interpolated from the linear range of concurrently run purified human IgG (Sigma-Aldrich) standard curves using Prism software, version 8.0 (GraphPad).
quantities of background +2 SDs. Each data point is the mean of technical duplicates.

**Fig. 4.** Peak vaccine-induced humoral immunity against SARS-CoV-2 S protein and RBD variant antigens is not affected by AZD7442 mAb coadministration. Electrochemiluminescence multiplex IgG binding responses against S protein and RBD WA1/2020, B.1.617.2, and B.1.1.529 variant antigens at peak immunogenicity (day 28) are shown. Solid red horizontal lines depict median quantities (n = 6 per group). Horizontal red dotted lines depict arbitrarily defined assay positivity threshold of mean background +2 SDs. Each data point is the mean of technical duplicates. Data were generated over several batch analyses of samples (N = 1 experiment). One-way ANOVA with Tukey’s correction was used for statistical analyses. *p < 0.05.

Lipofectamine 2000 (Thermo Fisher Scientific). Pseudo-viruses of SARS-CoV-2 variants were generated by using the WA1/2020 strain (Wuhan/WIV04/2019; Global Initiative on Sharing All Influenza Data (GISAID) accession ID: EPI_ISL_402124) or B.1.1.529 (Omicron; GISAID ID: EPI_ISL_7358094.2). The supernatants containing the pseudo-type viruses were collected 48 hours after transfection; pseudo-type viruses were purified by filtration with 0.45-μm filters. To determine the neutralization activity of human serum, HEK293T cells expressing human angiotensin converting enzyme 2 (HEK293T-hACE2 cells) were seeded in 96-well tissue culture plates at a density of 2.0 \times 10^4 cells per well overnight. Threefold serial dilutions of heat-inactivated serum samples were prepared and mixed with 50 μl of pseudo-virus. The mixture was incubated at 37°C for 1 hour before adding to HEK293T-hACE2 cells. After 48 hours, cells were lysed in the Steady-Glo Luciferase Assay (Promega) according to the manufacturer’s instructions. SARS-CoV-2 neutralization titers were defined as the sample dilution at which a 50% reduction (NT_{50}) in relative light units (RLU) was observed relative to the average of the virus control wells.

**Enzyme-linked immunosorbent assay**
SARS-CoV-2 RBD-specific binding antibodies in serum were assessed by ELISA. Ninety-six-well plates were coated with SARS-CoV-2 WA1/2020 RBD protein (1 μg/ml) in 1x Dulbecco’s PBS (DPBS) and incubated at 4°C overnight. After incubation, plates were washed once with wash buffer (0.05% Tween 20 in 1x DPBS) and blocked with 350 μl of casein block solution (Thermo Fisher Scientific) per well for 2 to 3 hours at room temperature. After incubation, block solution was discarded, and plates were blotted dry. Serial dilutions of heat-inactivated serum diluted in casein block were added to wells, and plates were incubated for 1 hour at room temperature, before three more washes and a 1-hour incubation at room temperature in the dark with a dilution (1 μg/ml) of anti-macaque IgG HRP (Nonhuman Primate Reagent Resource, AB_2819289) that does not cross-react with human IgG. Plates were washed three times, and 100 μl of SeraCare KPL TMB SureBlue Start solution was added to each well; plate development was halted by adding 100 μl of SeraCare KPL TMB Stop solution per well. The absorbance at 450 nm was recorded with a VersaMax microplate reader (Molecular Devices). For each sample, the ELISA endpoint titer was calculated using a four-parameter logistic curve fit to calculate the reciprocal serum dilution that yields an absorbance value of 0.2. Interpolated endpoint titers were reported.

**Electrochemiluminescence assay**
Electrochemiluminescence assay (ECLA) plates (MSD SARS-CoV-2) were designed and produced with up to 10 antigen spots in each well, including S proteins and RBDs from multiple SARS-CoV-2 variants. The plates were blocked with 50 μl of blocker A (1% bovine serum albumin in distilled water) solution for at least 30 min at room temperature shaking at 700 rpm with a digital microplate shaker. During blocking, the serum was diluted to 1:5000 or 1:50,000 in MSD diluent 100. The calibrator curve was prepared by diluting the calibrator mixture from MSD 1:10 in diluent 100 and then preparing a seven-step fourfold dilution series and a blank containing only MSD diluent 100. The plates were then washed three times with 150 μl of wash buffer (0.5% Tween 20 in 1× PBS) and blotted dry, and 50 μl of the diluted samples and calibration curve were added in duplicate to the plates and set to shake at 700 rpm at room temperature for at least 2 hours. The plates were again washed three times and 50 μl of SULFO-Tagged anti-human IgG detection antibody diluted to 1× in diluent 100 was added to each well; samples were then incubated with shaking at 700 rpm at room temperature for at least 1 hour. Plates were then washed three times and 150 μl of MSD GOLD Read Buffer B was added to each well; the plates were read immediately after on a Meso QuickPlex SQ 120 machine. MSD titers for each sample were reported as RLU, which were calculated as sample RLU minus blank RLU and then fit using a logarithmic fit to the standard curve. The upper limit of detection was defined as 2 \times 10^6 RLU for each assay. If the signal exceeded this value at 1:5000 serum dilution, then the sample was run again at 1:50,000, and the fitted RLU was multiplied by 10 before reporting. The lower limit of detection was defined as 1 RLU, and an RLU value of 100 was defined to be positive for each assay.
Intracellular cytokine staining

CD4+ and CD8+ T cell responses were quantitated by pooled peptide-stimulated intracellular cytokine staining assays. Peptide pools were 16 amino acid peptides overlapping by 11 amino acids spanning the SARS-CoV-2 WA1/2020 S protein (21st Century Biochemicals). Peripheral blood mononuclear cells (10⁶) per well were resuspended in 100 μl of R10 media (RPMI 1640 supplemented with 10% fetal bovine serum and penicillin-streptomycin) supplemented with CD49d mAb (1 μg/ml) and CD28 mAb (1 μg/ml). Each sample was stimulated with mock (100 μl of R10 plus 0.5% dimethyl sulfoxide; background control), peptides (2 μg/ml), or phorbol myristate acetate (10 pg/ml) and ionomycin (1 μg/ml; Sigma-Aldrich) (100 μl; positive control) and incubated at 37°C for 1 hour. After incubation, 0.25 μl of GolgiStop (BD Biosciences) and 0.25 μl of GolgiPlug (BD Biosciences) in 50 μl of R10 was added to each well; samples were incubated at 37°C for 8 hours and then held at 4°C overnight. The next day, the cells were washed twice with DPBS, stained with aqua LIVE/DEAD dye for 10 min, and then stained with predetermined titers of mAbs against CD279 (2 μl per test of clone EH12.1; Brilliant blue 700, BD Pharmingen), CD38 [0.5 μl per test with clone OKT10; phycoerythrin (PE), NHP Reagent Resource], 2.5 μl per test with CD28 (clone 28.2, PE-Cy5), CD4 [0.625 μl per test with clone L200; Brilliant Violet 510 (BV510), BD Pharmingen], and CD8 (1 μl per test with clone SK1; BUV805, BD Pharmingen) for 30 min. Cells were then washed twice with 1× Perm Wash buffer and fixed with 250 μl of freshly prepared 1.5% formaldehyde. Fixed cells were transferred to 96-well round-bottom plate and analyzed by BD FACSymphony system. Data were analyzed using FlowJo v9.9.

Surface plasmon resonance binding assay

Assays were performed using a Biacore 3000 (Cytiva) and HBS-EP immobilization buffer [0.01 M Hepes (pH 7.4), 0.15 M NaCl, 3 mM EDTA, and 0.005% (v/v) surfactant P20 (Cytiva)]. RhAd52-S.PP at 10¹¹ viral particles was diluted 1:5 in acetate 4.5 buffer (Cytiva) and immobilized on a C1 sensor chip. RU, response units.
chip using a standard amine coupling protocol. Multiple concentrations of AZD7442 (1000, 250, 500, 125, and 62.5 nM) were titrated over the sensor chip with an association time of 120 s and a dissociation time of 120 s at a flow rate of 50 μl/min. The surface was regenerated with a 30-s injection of 25 mM NaOH at a flow rate of 50 μl/min. All sensogram plots were subtracted from the reference flow cell and buffer cycle to remove nonspecific responses.

Statistics

Verification of normal data distribution was conducted using the Shapiro-Wilk normality test. Determination of significance where required was conducted using one-way analysis of variance (ANOVA) with Tukey’s correction for multiple comparisons. All statistics were performed using GraphPad Prism software version 9.3.1.

SUPPLEMENTARY MATERIALS

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Fig S1
Tables S1 to S8

Verification of normal data distribution was conducted using the Shapiro-Wilk normality test. Determination of significance where required was conducted using one-way analysis of variance (ANOVA) with Tukey’s correction for multiple comparisons. All statistics were performed using GraphPad Prism software version 9.3.1.

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