Coronavirus Disease 2019 Messenger RNA Vaccine Immunogenicity in Immunosuppressed Individuals

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Individuals on immunosuppressive (IS) therapy have increased mortality from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and delayed viral clearance may lead to new viral variants. IS therapy reduces antibody responses following coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccination; however, a comprehensive assessment of vaccine immunogenicity is lacking. Here we show that IS therapy reduced neutralizing, binding, and nonneutralizing antibody functions in addition to CD4 and CD8 T-cell interferon-γ responses following COVID-19 mRNA vaccination compared to immunocompetent individuals. Moreover, IS therapy reduced cross-reactivity against SARS-CoV-2 variants. These data suggest that the standard COVID-19 mRNA vaccine regimens will likely not provide optimal protection in immunocompromised individuals.

Keywords. immunocompromised; COVID-19 vaccine; SARS-CoV-2; vaccine immunogenicity; T cells.

Individuals on immunosuppressive (IS) therapy for autoimmune disease or transplantation face greater risks of mortality and morbidity from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The observation of prolonged SARS-CoV-2 replication in immunocompromised individuals has raised the question of immunologic control in such populations [1], and recent studies have shown that only 38%–54%

of kidney and liver transplant recipients developed detectable SARS-CoV-2 antibodies following the second dose of a coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccine [2–5]. Specific medications including antimetabolite therapy (mycophenolate, azathioprine), high-dose corticosteroids, or maintenance on a 3-medication (triple IS) regimen have been associated with lower odds of antibody response in transplant recipients [2–5]. Prior studies have not reported comprehensive immune profiling or responses to SARS-CoV-2 variants and have only studied limited types of immunosuppression. In this study, we assessed comprehensive antibody and T-cell profiles following COVID-19 mRNA vaccination in individuals on IS therapy for several medical indications.

METHODS

We conducted a cohort study of individuals ≥18 years of age who received the BNT162b2 (Pfizer/BioNTech) or mRNA-1273 (Moderna) COVID-19 vaccine from 19 December 2020 through 8 April 2021. The Beth Israel Deaconess Medical Center institutional review board approved this study (number 2021P000344) and the parent biorepository study (number 2020P000361); participants provided written informed consent. Immune responses were assessed at each vaccine dose and 2–8 weeks after the second dose using comprehensive humoral and cellular immune assays as previously described and detailed in the Supplementary Methods [6].

RESULTS

Ninety participants were enrolled for this study, including 69 participants who were receiving IS therapy for solid organ transplant, bone marrow transplant, and/or chronic inflammatory disease. Eight were excluded from the primary analysis due to known or suspected prior SARS-CoV-2 infection. Twenty-one participants not on IS therapy were enrolled as healthy controls. The 61 participants on IS therapy and without prior SARS-CoV-2 infection were stratified into 2 groups: 47 on single or double IS medications and 14 on triple IS medications. Sampling occurred a median of 24 days (interquartile range, 18–35 days) following the second mRNA vaccine, and most received the BNT162b2 vaccine. Fever following the second dose of vaccination was reported by 37% in the control group, 3% in the single/double IS group, and 0% in the triple IS group (Supplementary Table 1). No participants were diagnosed with new SARS-CoV-2 infection during the study.

Antibody responses were assessed by pseudovirus neutralization assays, receptor binding domain (RBD)–specific enzyme-linked immunosorbent assays, and Fc functional antibody assays. The median neutralizing antibody titer (NT_{50}) was 955
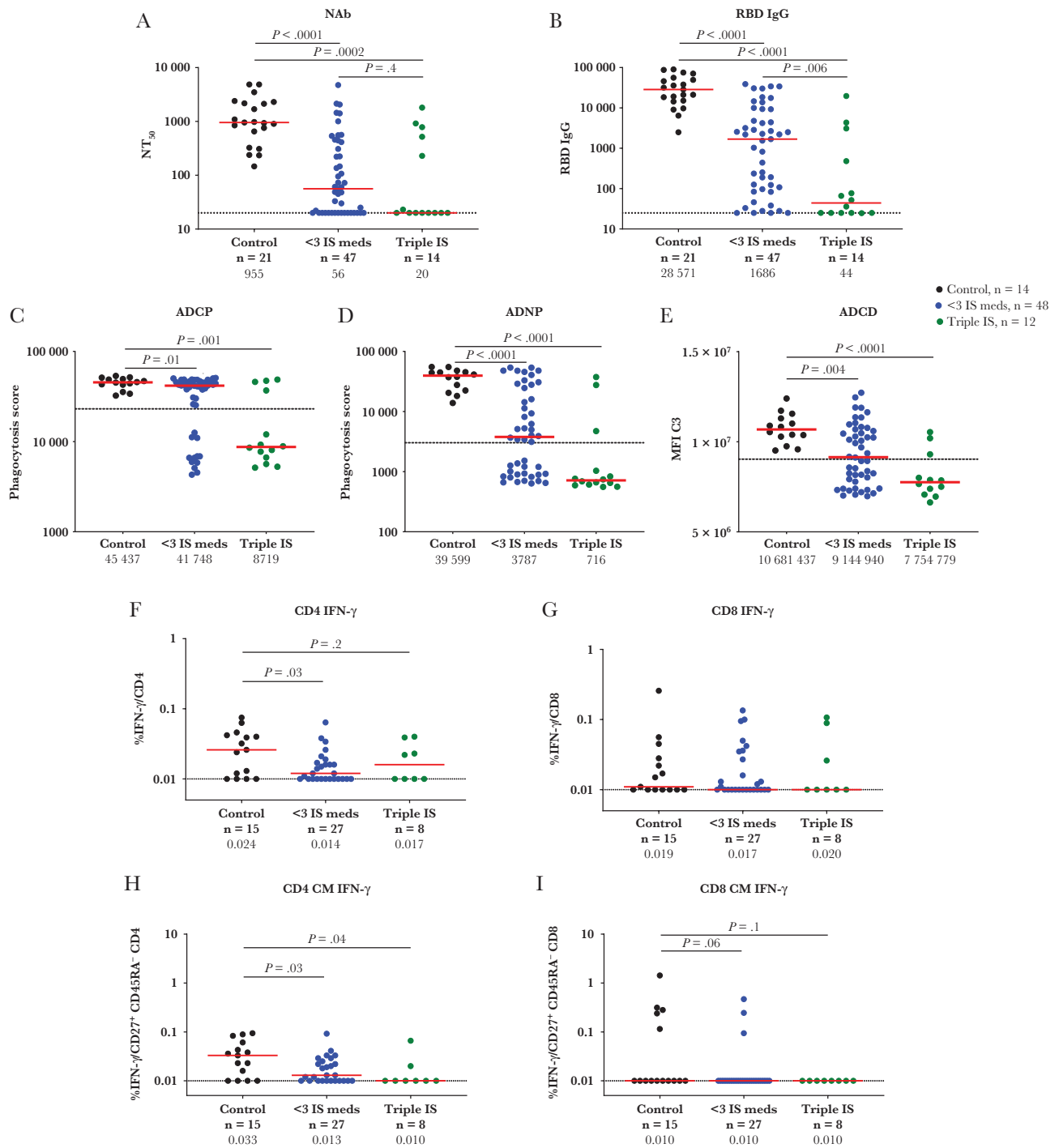
Figure 1. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody and T-cell activity following coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccination in individuals on immunosuppressive (IS) therapy. Pseudovirus neutralizing antibody titers (NT_{50}) (*A*) and SARS-CoV-2 spike receptor-binding domain (RBD) immunoglobulin G titer (*B*) 2–8 weeks following second dose of COVID-19 mRNA vaccination in individuals on single/double IS therapy (blue), on triple IS therapy (green), and controls (black). Systems serology was used to quantify RBD-specific antibody-dependent monocyte cellular phagocytosis (*C*), antibody-dependent neutrophil phagocytosis expressed as a phagocytosis score (*D*), and mean fluorescence index of complement component 3 for antibody-dependent complement deposition (*E*). Peripheral blood mononuclear cells at 2–8 weeks following second dose of COVID-19 mRNA vaccination in all 3 groups. T-cell responses were measured using multiparameter intracellular cytokine staining to measure percentage interferon-γ production in CD4 T cells (*F*), CD8 T cells (*G*), and by CD45RA⁻CD27⁺ central memory (CM) CD4 T cells (*H*) and CD8 CM T cells (*I*). Medians (red bar) are displayed below each time point on the x-axis. Dotted line indicates limit of detection, and the dashed line in *C–E* indicates line of positivity. Abbreviations: ADCD, antibody-dependent complement deposition; ADCP, antibody-dependent monocyte cellular phagocytosis; ADNP, antibody-dependent neutrophil phagocytosis; CM, central memory; IFN-γ, interferon gamma; IgG, immunoglobulin G; IS, immunosuppressive; MFI C3, mean fluorescence index of complement component 3; NAb, neutralizing antibody; NT_{50}, median neutralizing antibody titer; RBD, receptor-binding domain.
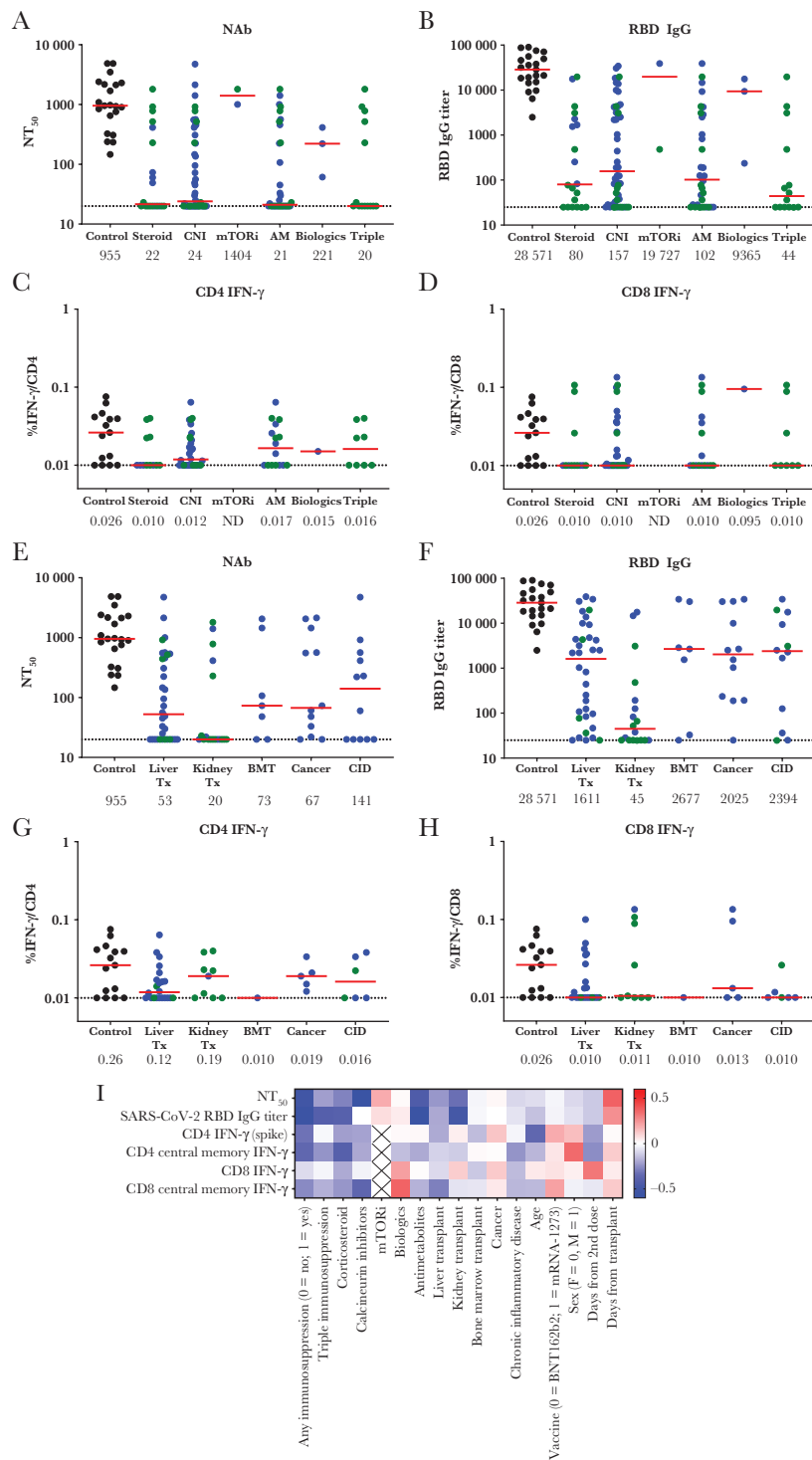
Figure 2. Humoral and cellular immune responses in individuals on immunosuppressive (IS) therapy stratified by clinical characteristics (medications and indication for therapy). Pseudovirus neutralizing antibody titers (NT$_{50}$) (*A* and *E*) and receptor-binding domain immunoglobulin G binding antibody titers (*B* and *F*) were measured in serum at 2–8 weeks following second dose of coronavirus disease 2019 messenger RNA vaccination in individuals on single/double IS therapy (blue), those on triple IS therapy (green), and controls (black). T-cell responses were measured using intracellular cytokine staining to measure percentage interferon gamma (IFN-γ) production in CD4 T cells (*C* and *G*) and CD8 T cells (*D* and *H*). Median antibody titers or percentage IFN-γ production (red bar, and listed below x-axis) and the limit of detection (dotted line) are shown. Results are stratified by non–mutually exclusive categories of medication use (*A–D*) and by medical indication for IS therapy (*E–H*). "Biologic therapy" included rituximab and infliximab. Heatmap of Spearman correlation coefficient values for correlation between clinical variables on the x-axis and 6 vaccine-induced immune parameters on the y-axis. Red indicates positive and blue indicates negative correlation (*I*). Abbreviations: AM, antimetabolite therapy (eg, mycophenolate, azathioprine, or leflunomide); BMT, bone marrow transplant; CID, chronic inflammatory disease; CNI, calcineurin inhibitor; F, female; IFN-γ, interferon gamma; IgG, immunoglobulin G; M, male; mTORi, mammalian target of rapamycin inhibitor; NAb, neutralizing antibody; NT$_{50}$, median neutralizing antibody titer; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Tx, transplantation.

in healthy controls, 56 in the single/double IS group, and <20 in the triple IS group ($P < .001$) (Figure 1A). NT_{50} titers were detected in 100% of healthy controls, in 66% of the single/double IS group, and in 36% of the triple IS group (Supplementary Table 2). Median RBD binding titers (Figure 1B) and functional nonneutralizing antibody responses (Figure 1C–E), including antibody-dependent cellular phagocytosis, antibody-dependent neutrophil phagocytosis, and antibody-dependent complement deposition, were also reduced in the single/double IS group and were markedly reduced in the triple IS group.

Corticosteroids, calcineurin inhibitors, antimetabolites, triple IS therapy, and kidney transplant were associated with particularly low or undetectable NT_{50} titers of 49, 28, <20, and <20, respectively (Figure 2A–H), and were all strongly correlated with reduced immune responses (Figure 2I). The 8 participants with prior SARS-CoV-2 infection displayed a high median NT_{50} titer of 3083 and a high median RBD-specific binding antibody titer of 38 058 following vaccination (Supplementary Figure 1).

Median spike-specific interferon gamma (IFN-γ) CD4 T-cell responses were 0.024% in healthy controls, as compared with 0.014% and 0.017% in the single/double IS and triple IS groups, respectively (Figure 1F, Supplementary Table 2). A similar pattern was observed for central memory CD4 T cells (Figure 1H). IFN-γ spike-specific CD8 T-cell responses were detectable but low in all groups (Figure 1G and 1I).

Humoral and cellular responses also were reduced against viral variants in individuals on IS therapy (Supplementary Figure 2). Neutralizing and binding antibody responses were typically observed in immunocompetent individuals against the SARS-CoV-2 B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and other variants. Responses to all variants were reduced in the single/double IS group but were nearly ablated in the triple IS group.

DISCUSSION

This study demonstrates markedly reduced humoral and cellular immunogenicity of mRNA COVID-19 vaccines in individuals on IS therapy compared with healthy controls. Multiple immune parameters were decreased, including neutralizing, binding, and functional nonneutralizing antibodies, as well as T-cell responses against both the original vaccine strain and against multiple viral variants. Suppression of vaccine immunogenicity was particularly striking in individuals on triple IS therapy.

Our findings extend prior studies that have recently reported reduced spike-specific antibodies [3, 4, 7] and T-helper responses [8] in transplant recipients following COVID-19 mRNA vaccination. In this study, we show that multiple humoral and cellular immune parameters as well as coverage of viral variants were simultaneously diminished. These observations suggest that there will likely be reduced efficacy of mRNA COVID-19 vaccines for individuals on IS medications. Prior

studies have estimated efficacy of 59% compared to 91% in immunocompetent individuals [9], and another study in Israel demonstrated that those on IS therapy represented 40% of breakthrough infections [10]. In our study, suppression of vaccine immunogenicity was particularly striking in individuals on antimetabolites, calcineurin inhibitors, or corticosteroids, or with kidney transplant. Moreover, we observed substantially more suppression of vaccine immunogenicity in individuals on triple IS therapy, suggesting that these populations may be at highest risk of COVID-19 vaccine breakthrough infections.

Recent data support a third dose of mRNA vaccines to boost immunity in transplant recipients [11], and the FDA recently approved use of a third mRNA vaccine dose for immunocompromised individuals [12]. It is currently not known if a third mRNA dose will be immunogenic in individuals on triple IS therapy and will improve protective efficacy.

This study has several limitations. First, the small study size limits definitive conclusions about vaccine tolerability or clinical efficacy and limits the ability to indication for immunosuppression. Second, immune responses were evaluated at a short interval following vaccination; thus, we cannot make conclusions about the durability of immune responses. Third, this was a clinical cohort study rather than a randomized controlled trial.

In conclusion, although analysis of the mRNA-1273 phase 3 trial participants suggests that antibody levels after vaccination correlate to protection against COVID-19 [13] in humans, it is unclear whether or not this would apply to other vaccine platforms or in a population of individuals on medical immunosuppression. The marked suppression of both humoral and cellular immune responses in certain subsets of immunosuppressed individuals suggests that these populations will likely not be protected by the 2-dose regimens of mRNA COVID-19 vaccines.

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