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Reduced Immune Response to Inactivated Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine in a Cohort of Immunocompromised Patients in Chile

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Background. Inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines have been widely implemented in low- and middle-income countries. However, immunogenicity in immunocompromised patients has not been established. Herein, we aimed to evaluate immune response to CoronaVac vaccine in these patients.

Methods. This prospective cohort study included 193 participants with 5 different immunocompromising conditions and 67 controls, receiving 2 doses of CoronaVac 8–12 weeks before enrollment. The study was conducted between May and August 2021, at Red de Salud UC-CHRISTUS, Santiago, Chile. Neutralizing antibody (NAb) positivity, total anti–SARS-CoV-2 immunoglobulin G antibody (TAb) concentrations, and T-cell responses were determined.

Results. NAb positivity and median neutralizing activity were 83.1% and 51.2% for the control group versus 20.6% and 5.7% (both $P < .001$) in the solid organ transplant group, 41.5% and 19.2% (both $P < .0001$) in the autoimmune rheumatic diseases group, 43.3% ($P < .001$) and 21.4% ($P<.01$ or $P = .001$) in the cancer with solid tumors group, 45.5% and 28.7% (both $P < .001$) in the human immunodeficiency virus (HIV) infection group, 64.3% and 56.6% (both differences not significant) in the hematopoietic stem cell transplant group, respectively. TAb seropositivity was also lower for the solid organ transplant (20.6%; $P < .0001$), rheumatic diseases (61%; $P < .001$), and HIV groups (70.9%; $P = .003$), compared with the control group (92.3%). On the other hand, the number of interferon γ spot-forming T cells specific for SARS-CoV-2 tended to be lower in all immunocompromising conditions but did not differ significantly between groups.

Conclusions. Diverse immunocompromising conditions markedly reduce the humoral response to CoronaVac vaccine. These findings suggest that a boosting vaccination strategy should be considered in these vulnerable patients.

Clinical Trials Registration. NCT04888793.

Keywords. SARS-CoV-2; COVID-19; CoronaVac; inactivated vaccine; immunocompromised patient.

The coronavirus disease 2019 (COVID-19) pandemic has ravaged across the globe, claiming >4 million lives [1]. New vaccine platforms, such as adenovirus vectored and nucleic acid vaccines, have succeeded in inducing robust cellular and humoral immune responses [2]. Novel messenger RNA (mRNA) vaccines, such as BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), have demonstrated a stunning >94% efficacy against COVID-19 [3, 4]. However, many low- and middle-income countries have had access to conventional inactivated vaccines approved under emergency use, such as CoronaVac (Sinovac), BBIBP-CorV (Sinopharm Beijing), or BBV152 (Bharat Biotech) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines [5].

Inactivated vaccines have demonstrated relatively lower levels of neutralizing antibodies (NAbs) and T-cell responses compared with other vaccines, and must be assisted by adjuvants with ≥1 booster to establish immunological memory [2]. A preliminary study in healthy individuals showed lower NAb concentrations

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obtained by CoronaVac compared with mRNA-based vaccine [6]. This is relevant, since NAbs could predict immune protection after SARS-CoV-2 vaccination and in vitro neutralization titers remain a correlate of protection from SARS-CoV-2 variants [7, 8].

In Chile, COVID-19 was first detected in March 2020. Eighteen months later, official numbers reached >1.6 million confirmed cases and >37 000 deaths. As of 2 January 2021, >90% of Chile's target population have received 2 vaccine doses, and CoronaVac has been the main vaccine, used in >70% of cases [9]. A phase III trial in 18–59-year-old participants indicated 83.5% CoronaVac efficacy against symptomatic COVID-19 [10]. Locally, the reported prevention and mortality effectiveness rates were 65.9% and 86.3%, respectively [11].

Immunocompromised patients represent a vulnerable population at higher risk of severe COVID-19 and death from COVID-19, and there are very limited data on efficacy of SARS-CoV-2 vaccines in these patients. The present study aimed to evaluate the immune response induced by an inactivated anti–SARS-CoV-2 vaccine, CoronaVac, in adults with different acquired immunosuppressing conditions, compared with healthy volunteers.

METHODS

Study Population and Design

Adult patients with predefined acquired immunosuppressive conditions under medical care at Red de Salud UC-CHRISTUS (Santiago, Chile) and collaborating centers (Hospital Clínico Universidad de Chile, Santiago, Chile), having received 2 doses of CoronaVac vaccine separated by 4 weeks (standard schedule) with the second dose administered 8–12 weeks before enrollment, were invited to participate between 12 May and 6 August 2021. In addition, participants without immunosuppression vaccinated with 2 doses of CoronaVac during the same time period, were selected for the control arm. Patients reporting previous SARS-CoV-2 infection or having received plasma or intravenous immunoglobulin therapy in the previous 60 days were excluded.

Specific inclusion criteria were as follows: (1) cancer cohort: diagnosis of solid tumor (excluding leukemias, lymphomas, or multiple myelomas) and current chemotherapy; (2) hematopoietic stem cell transplant (HSCT) cohort: allogeneic transplantation with active immunosuppressive treatment or autologous transplantation, within the last 5 years; (3) solid organ transplant (SOT) cohort: liver, kidney, or heart transplantation within the last 5 years, with active immunosuppressive treatment; (4) human immunodeficiency virus (HIV) cohort: HIV infection under antiretroviral therapy with CD4 cell counts ≤500/μL and HIV viral load <200 copies/mL; and (5) autoimmune rheumatic diseases cohort: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, relapsing polychondritis, Behcet disease, or juvenile idiopathic arthritis and long-term immunomodulatory treatment with anti–tumor necrosis factor (TNF), anti–interleukin 6, or anti–interleukin 17 agents.

Blood Sampling

A single blood sample was collected between 8 and 12 weeks (±72 hours) after the second dose of CoronaVac vaccine.

Outcomes

The primary outcome was humoral immunogenicity assessed by the proportion of participants with positive SARS-CoV-2 NAb results 8–12 weeks after receiving the CoronaVac vaccine. Secondary immunogenicity outcomes included the percentage of neutralizing activity, expressed as the inhibition percentage of NAb; immunoglobulin G (IgG) seropositivity, measured as the total IgG anti–spike protein 1 (S1) domain of SARS-CoV-2 (total anti–SARS-CoV-2 IgG antibody [TAb]); the geometric mean concentration (GMC) of anti–S1 IgG; and the specific T-cell immune response to SARS-CoV-2 antigens. The study was registered with ClinicalTrials.gov (NCT04888793).

Laboratory Assessments

Determination of Anti–SARS-CoV-2 IgG Antibodies

A commercial enzyme-linked immunosorbent assay (SARS-CoV-2 QuantiVac; Euroimmun) was used for quantitative in vitro determination of human TAbs in serum samples. Data were expressed in relative units (RU) per milliliter, and values ≥11 RU/mL were interpreted as positive, according to the manufacturer's instructions.

Determination of NAbs Against SARS-CoV-2

The presence of NAbs against SARS-CoV-2 was determined using a SARS-CoV-2 surrogate virus neutralization test (sVNT) kit (GenScript), according to the manufacturer's instructions. The test assesses the presence or absence of NAbs, and the inhibition rate is defined as [1 – (optical density [OD] of sample/OD of negative control)] × 100%. Neutralization of ≥30% at a 1:10 sample dilution was considered a positive result.

The assessment of variant of concern neutralization was performed using an sVNT developed based on previous reports [12]. Receptor-binding domain unconjugated proteins from SARS-CoV-2 variant D614G were obtained from GenScript (no. Z03483), and P.1-Gamma variant from SinoBiological (no. 40592-V08H86). The percentage of inhibition was defined as (OD_{450} of negative control – OD_{450} of sample)/(OD_{450} of negative control × 100), where OD_{450} indicates OD at 450 nm.

Cellular Immunity Assessments

The presence of interferon (IFN) γ spot-forming cells (SFCs) specific for SARS-CoV-2 was determined with human IFN-γ/interleukin 4 (IL-4) double-color enzyme-linked immunospot assay (Immunospot), using isolated peripheral

blood mononuclear cells, obtained as described elsewhere [13]. T cells were stimulated with megapools (MPs) of peptides derived from the SARS-CoV-2 proteome, which include 2 sets of 15-mer peptides derived from the spike protein (MP-S) and the remaining proteins (MP-R) and 2 sets of 8–9-mer peptides derived from the whole proteome, as described elsewhere [14]. A total of 3×10^5 cells were incubated with each respective stimulus and incubated for 48 hours at 37°C and 5% carbon dioxide [13]. As positive controls, peripheral blood mononuclear cells were stimulated with concanavalin A and MPs of peptides derived from cytomegalovirus, and stimulation with dimethyl sulfoxide (DMSO) 1% was included as a negative control to determine unspecific response. IFN-γ/IL-4 production was measured as indicated by the manufacturer, and SFCs were counted on an ImmunoSpot S6 Micro Analyzer. SFCs obtained in DMSO stimulation were subtracted from those obtained for each MP stimulation and expressed as SFCs per 3×10^5 cells.

Statistical Analyses

The sample size was calculated with a significance level of 5% and a statistical power of 90% to detect differences of 15% in postvaccine NAb seropositivity for immunocompromised patients compared with the control group. The seropositivity in the immunocompetent population was estimated to be 97%, according to the results of the phase I/II study of the CoronaVac vaccine 28 days after vaccination [15]. The total number of patients to be recruited was 86 for each study arm, with a total of 516 participants. Dichotomous variables were compared using χ^2 or Fisher exact tests, and continuous variables using *t* or Mann-Whitney tests. Confounding effects and effect modifier of potential covariates, such as age, body mass index and time from vaccination, were explored using generalized linear models. Binary variables, such as seropositivity in NAb or TAb, were analyzed with logistic regression, and the NAb inhibition percentage was examined using a β regression model.

The quantitative measurement of anti–SARS-Cov2 IgG antibodies was expressed in geometric means and analyzed with generalized linear models, with gaussian family and identity link functions, respectively. Exponentiated coefficients of the log-transformed dependent variable provided the effects of the covariates on the geometric mean. These models were chosen based on the characteristics of the dependent variables as well as their goodness of fit using the Akaike information criterion. Analyses and graphs were performed using STATA (version 14) and GraphPad Prism 9.0.1 software.

Ethics

This study was approved by the institutional review board of the Pontificia Universidad Católica de Chile. Informed consent was obtained from all patients.

RESULTS

Description of Cohorts

A total of 260 healthy individuals and patients with immunocompromising conditions consented to this study. We excluded a total of 21 participants who were found not to fulfill protocol inclusion/exclusion criteria. Thus, final groups of analysis included 65 healthy controls, 34 SOT recipients, 41 patients with rheumatic disease, 30 with solid-tumor cancer, 55 HIV-infected patients and 14 HCST recipients (Figure 1). Clinical and epidemiological characteristics of enrolled patients are provided in Table 1.

Humoral Immune Response

The proportion of individuals with positive NAb and TAb results were 40.8% and 63.8%, respectively, for all immunocompromised patients, compared with 83.1% and 92.3% in the control group ($P < .001$). The proportion of patients who reached NAb positivity and the amount of neutralizing activity were significantly lower in all immunocompromised cohorts compared with the control group, except for the HSCT group (Figure 2A and 2B). Neutralizing response was particularly impaired in the SOT group, with only 20.6% of participants reaching an NAb-positive response and with a median neutralizing activity of 5.66% (interquartile range, 3.7%–11.7%) versus 51.21% (34.6%–68.6%) in the control group ($P < .001$). Multivariable analysis adjusting for age, body mass index, and time from vaccination to blood sampling did not modify these findings (Table 2).

TAb positivity and concentrations were also significantly lower in the SOT (20.6% and GMC of 5.6 AU/mL; both $P < .001$), rheumatic diseases (61% and 15.2 RU/mL; both $P < .001$) and HIV (70.9% and 21.2 RU/mL; both $P < .005$)

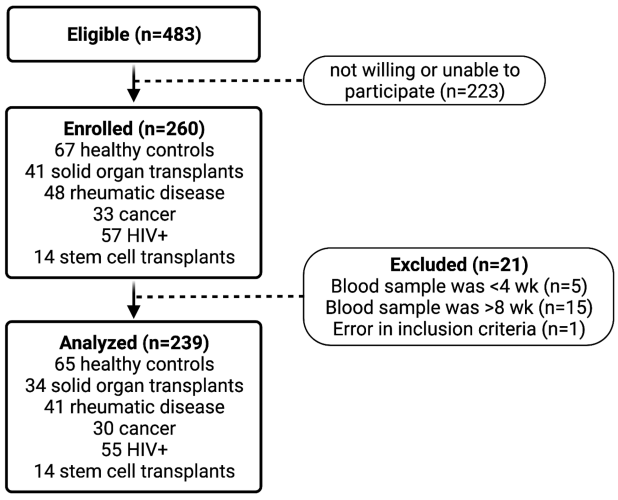

Figure 1. Study flow chart. Abbreviations: HIV+, human immunodeficiency virus infected; HSCT, hematopoietic stem cell transplant; SOT, solid organ transplant.

Table 1. Baseline Characteristics of Enrolled Participants in Immunocompromised and Control Groups

Characteristic	Participants by Group, No. (%)[a]					
	Controls (n = 65)	SOT (n = 34)	Rheumatic Diseases (n = 41)	Cancer (n = 30)	HIV Infected (n = 55)	HSCT (n = 14)
Demographics						
Age (y), mean (range)	44.3 (51.0)	54.0 (54.0)	51.7 (45.0)	57.7 (46.0)	46.8 (52.0)	47.4 (49.0)
Female sex	44 (67.7)	16 (47.1)	30 (73.2)	17 (56.7)	2 (3.6)	4 (28.6)
Current smoking	12 (18.5)	1 (2.9)	8 (19.5)	2 (6.7)	17 (30.9)	0 (0.0)
BMI, mean (SD)[b]	24.7 (4.2)	28.1 (6.6)	29.5 (4.9)	25.7 (3.4)	26.9 (3.7)	28.8 (6.0)
Comorbid conditions						
Hypertension	4 (6.2)	14 (41.2)	15 (36.6)	8 (26.7)	9 (16.4)	2 (14.3)
Diabetes	1 (1.5)	10 (29.4)	6 (14.6)	8 (26.7)	6 (10.9)	2 (14.3)
Asthma or COPD	5 (7.7)	0 (0.0)	4 (9.8)	1 (3.3)	3 (5.5)	0 (0.0)
Chronic renal disease	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chronic liver disease	0 (0.0)	3 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Current immunosuppressive or immunomodulator therapy						
Prednisone	…	23 (67.6)	22 (53.7)	0 (0.0)	1 (1.8)	0 (0.0)
Prednisone dose >15 mg/d	…	3 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hydroxichloroquine	…	0 (0.0)	8 (19.5)	0 (0.0)	0 (0.0)	0 (0.0)
Sulphasalazine	…	0 (0.0)	7 (17.1)	0 (0.0)	0 (0.0)	0 (0.0)
Leflunomide	…	1 (2.9)	10 (24.4)	0 (0.0)	0 (0.0)	0 (0.0)
Methotrexate	…	0 (0.0)	20 (48.8)	0 (0.0)	0 (0.0)	3 (21.4)
Mycophenolate mofetil	…	25 (73.5)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Tacrolimus	…	30 (88.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)
Cyclosporine	…	3 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)
TNF inhibitors[c]	…	…	40 (97.6)	…	…	…
Anti–IL-6 (tocilizumab)	…	…	1 (2.4)	…	…	…
Anti–IL-17 (secukinumab)	…	…	0 (0.0)	…	…	…
Cancer chemotherapy	…	…	…	30 (100)	…	…
Induction immunosuppressive therapy						
Basiliximab	…	19 (55.9)	…	…	…	…
Anti-thymocyte globulin	…	4 (11.8)	…	…	…	…
Antibody-mediated rejection therapy						
Anti-CD20 (rituximab)	…	2 (5.9)	…	…	…	…
Anti-thymocyte globulin	…	1 (2.9)	…	…	…	…
Time since transplant						
≤1 y	…	29 (85.3)	…	…	…	10 (71.4)
1 to ≥3 y	…	4 (11.8)	…	…	…	4 (28.6)
>3 to 5 y	…	1 (2.9)	…	…	…	0 (0.0)
Type of cancer						
Colorectal	…	…	…	14 (46.6)	…	…
Breast	…	…	…	6 (20.0)	…	…
Pancreas	…	…	…	2 (6.7)	…	…
Lung	…	…	…	2 (6.7)	…	…
Other[d]	…	…	…	6 (19.8)	…	…
Rheumatic diseases						
Rheumatoid arthritis	…	…	31 (75.6)	…	…	…
Psoriatic arthritis	…	…	9 (22.0)	…	…	…
Juvenile idiopathic arthritis	…	…	1 (2.4)	…	…	…
Type of transplant						
Liver	…	20 (58.8)	…	…	…	…
Kidney	…	11 (32.4)	…	…	…	…
Liver and kidney	…	2 (5.9)	…	…	…	…
Kidney and pancreas	…	1 (2.9)	…	…	…	…
Allogeneic HSCT	…	…	…	…	…	5 (35.7)
Autologous HSCT	…	…	…	…	…	9 (64.3)
CD4 cell count, mean (SD), cells/μL	…	…	…	…	358.8 (100.0)	…

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplant; IL-6, interleukin 6; IL-17, interleukin 17; SD, standard deviation; SOT, solid organ transplant; TNF, tumor necrosis factor.

[a]Data represent no. (%) of participants unless otherwise specified.

[b]BMI calculated as weight in kilograms divided by height in meters squared.

[c]TNF inhibitors include infliximab, golimumab, adalimumab, etanercept, and certolizumab pegol.

[d]Other cancers include peritoneum, gastric, liver, ovarium, testicular, and small-bowel cancer.

groups, compared with the control group (92.3% and 36.8 RU/mL) (Figure 2C and 2D). TAb seropositivity in cancer and HSCT groups did not differ from that in the control group. These findings were consistent in multivariable analysis (Table 2).

As an exploratory analysis, we evaluated other covariables that would affect the humoral response. We found that a negative NAb result was strongly associated with the use of prednisone (87.32% vs 12.68%; $P = .001$) and mycophenolate (71.43% vs 28.57%; $P = .007$). For all study participants, we found a strong correlation between TAb concentration and NAb neutralizing activity expressed as inhibition percentage ($r = 0.864$; $P < .001$), with an area under the receiver operating characteristic curve of 0.965 (95% confidence interval, .943–.988) and a TAb cutoff of ≥26 RU/mL best predicting NAb seropositivity (92% sensitivity and 94% specificity) (Supplementary Figure 1).

The neutralization capacity against the SARS-CoV-2 variants D614G and Gamma was tested in 9–13 serum samples from control and immunosuppressed patients with a positive NAb response in previous assays. These studies were performed using an sVNT that evaluated the capacity of serum to inhibit the binding of receptor-binding domains from these SARS-CoV-2

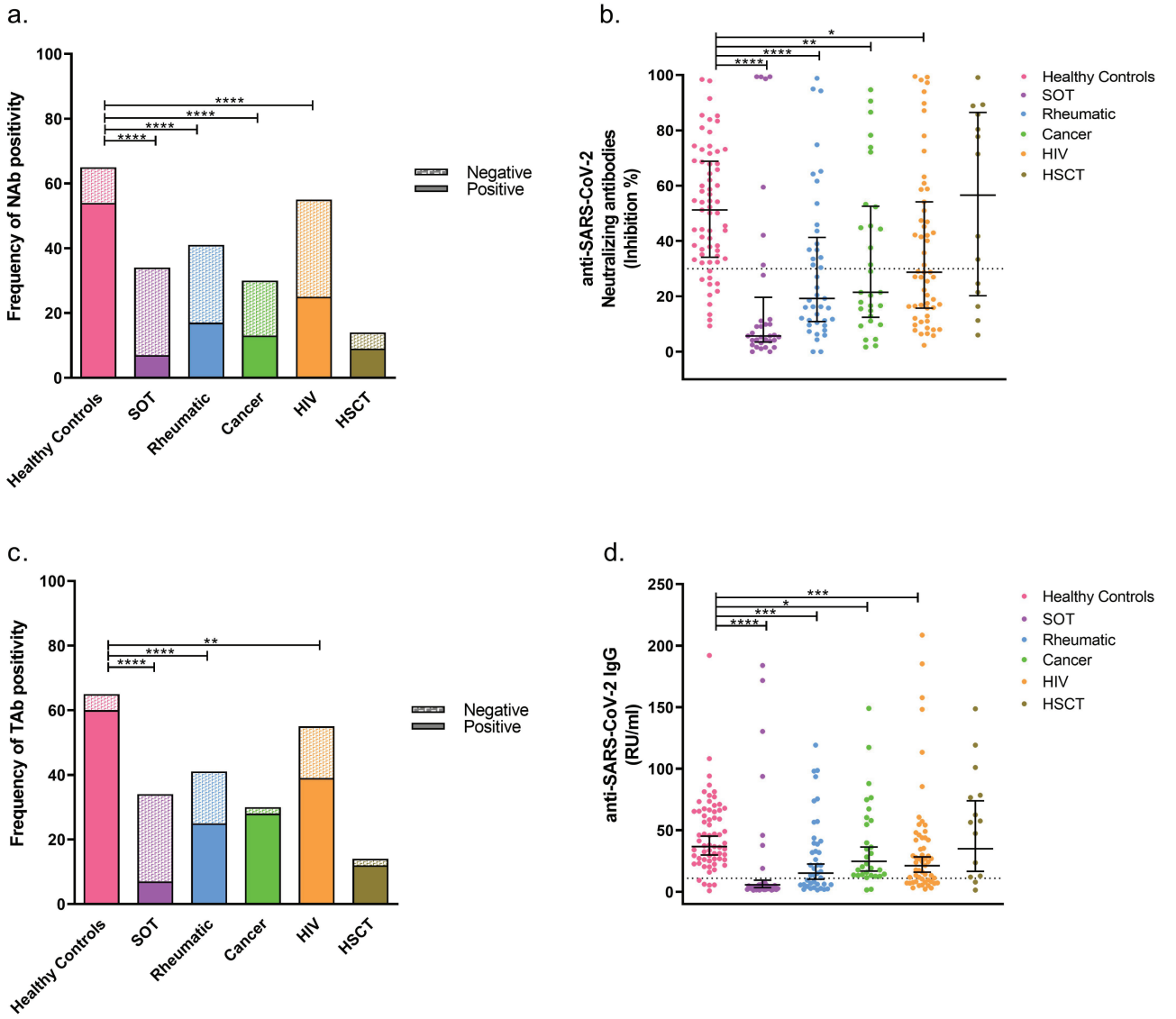

Figure 2. Humoral response against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in healthy and immunocompromised individuals 8–12 weeks after vaccination with CoronaVac. *A,* Frequency of neutralizing antibody (NAb) positivity (≥30% of inhibition rate). *B,* Neutralizing activity (percent of inhibition), displayed as median with interquartile range. *C,* Frequency of total anti–SARS-CoV-2 immunoglobulin G (TAb) positivity (≥11 relative units [RU]/mL). *D,* TAb geometric mean concentrations (GMCs) (with 95% confidence intervals). Comparison groups included healthy controls (n = 65) and solid organ transplant (SOT) (n = 34), rheumatic diseases (n = 41), cancer (n = 30), human immunodeficiency virus–infected (HIV+) (n = 55), and hematopoietic stem cell transplant (HSCT) (n = 14) groups. Dotted lines in *B* and *D* represent seropositivity cutoff. Statistical significance was calculated with Fisher (*A, C*) or Mann-Whitney (*B, D*) tests, and 2-tailed *P* values are indicated where significant. **P* ≤ .05; ***P* ≤ .01; ****P* ≤ .001; *****P*<.0001.

Table 2. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Neutralizing Antibody Positivity, Neutralizing Activity, Total Anti–SARS-CoV-2 Immunoglobulin G Antibody (TAb) Positivity, and TAb Geometric Mean Concentrations 8–12 Weeks After the Second CoronaVac Dose in Patients With Immunosuppression Conditions, Compared With Controls

		NAb Positivity[a]			Neutralizing Activity			TAb Positivity[b]		TAb Quantification	
Patient Group	Noyh,,. (%)	OR (95% CI); *P* Value[c]	aOR (95% CI); *P* Value[c]	Median (IQR), Inhibition %	ß Regression; *P* Value[c]	Adjusted ß Regression; *P* Value[c]	No. (%)	OR (95% CI); *P* Value[c]	GMC, RU/mL (95% CI)	ß Regression; *P* Value[c]
Controls (n = 65)	54 (83.1)	…	…	51.21 (34.6–68.6)	…	…	60 (92.3)	…	36.77 (30.0–45.05)	…
SOT (n = 34)	7 (20.6)	0.05 (.02–.15); <.001	0.07 (.02–.19); <.001	5.65 (3.67–11.7)	−1.23; <.001	−0.28; <.001	7 (20.6)	0.02 (.01–.07); <.001	5.64 (3.45–9.24)	0.15; <.001
Rheumatic diseases (n = 41)	17 (41.5)	0.14 (.06–.35); <.001	0.19 (.07–.49); .001	19.23 (11.27–38.98)	−0.82; <.001	−0.19; <.001	25 (61.0)	0.13 (.04–0.39); <.001	15.17 (10.36–22.22)	0.41; <.001
Cancer (n = 30)	13 (43.3)	0.15 (.06–.41); <.001	0.18 (.06–.49); .001	21.44 (12.86–52.34)	−0.60; .002	−0.14; .002	28 (93.3)	1.17 (.21–6.39); .86	24.71 (17.04–35.82)	0.67; .06
HIV infected (n = 55)	25 (45.5)	0.17 (.07–.39); <.001	0.19 (.08–.44); <.001	28.72 (15.74–54.13)	−0.39; .03	−0.09; .03	39 (70.9)	0.20 (.07–.60); .004	21.20 (15.98–28.13)	0.58; .002
HSCT (n = 14)	9 (64.3)	0.37 (.10–1.31); .12	0.45 (.12–1.71); .24	56.57 (21.46–85.71)	0.11; .74	0.02; .74	12 (85.7)	0.50 (.09-2.89); .44	34.98 (17.75–68.97)	0.95; .89

Neutralizing activity is expressed as inhibition percentage.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; GMC, geometric mean concentration; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplant; IQR, interquartile range; NAb, neutralizing antibody; OR, odds ratio; RU, relative units; SOT, solid organ transplant; TAb, total anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulin G antibody.

[a]Number of participants reaching the cutoff (≥30%) for NAb test positivity.

[b]Number of participants reaching the TAb cutoff (≥11 RU/mL).

[c]All *P* values represent comparisons with the control group.

variants to the recombinant angiotensin-converting enzyme 2 receptor. As shown in Supplementary Figure 2*A*, a significant reduction in neutralization of the D614G variant was observed in the rheumatic diseases and cancer groups, compared with control. For neutralization of the Gamma variant, a higher level was observed in the SOT group than in the control group (Supplementary Figure 2*B*). Inhibition levels for the Gamma variant show a significant reduction compared with that observed for the D614G for all groups except the SOT group (Supplementary Figure 2*C*).

Cellular Immune Response

Subgroups of enrolled patients were evaluated for IFN-γ SFCs on stimulation with MPs of SARS-CoV-2–derived peptides. As shown in Figure 3, the IFN-γ response in the immunocompromised groups when stimulated with 15-mer peptides (MP-S + MPR; Figure 3A) or 8–9-mer peptides (CD8A + CD8B; Figure 3B) tended to be lower than in the controls, but not significantly. Similarly, no significant differences were observed between groups for IL-4 SFCs (Supplementary Figure 3).

Patient Follow-up

Four nonsevere breakthrough COVID-19 cases occurred in enrolled participants (1.5%) from different groups after a mean period of 14 weeks following full vaccination. Two of these breakthrough cases occurred in patients with negative TAb and NAb results.

DISCUSSION

Our study demonstrates that humoral immune response induced by inactivated SARS-CoV-2 vaccine CoronaVac is significantly reduced in patients with immunocompromising conditions. As reported with other currently available vaccines, our findings are coherent with a higher-than-expected rate of breakthrough SARS-CoV-2 infections reports in immunocompromised patients [16]. Given these findings, vaccinated immunocompromised patients should consider continuing nonpharmaceutical interventions such as mask wearing, social distancing in personal, work, and clinical settings, and avoiding crowded settings [17].

Vaccine responses were markedly reduced in SOT recipients, with only 20% attaining a positive neutralizing response. These patients—who require life-long immunosuppression regimens and sometimes highly immunosuppressive induction therapy—also develop a weak humoral and cellular response after 2 doses of mRNA vaccine, with described TAb seropositivity ranging between 19% and 50% [18–20]. A previous study found that <10% reached a positive neutralizing response with 2 doses of mRNA vaccine [21]. Accordingly, cohort and population studies describe higher rates for COVID-19 breakthrough

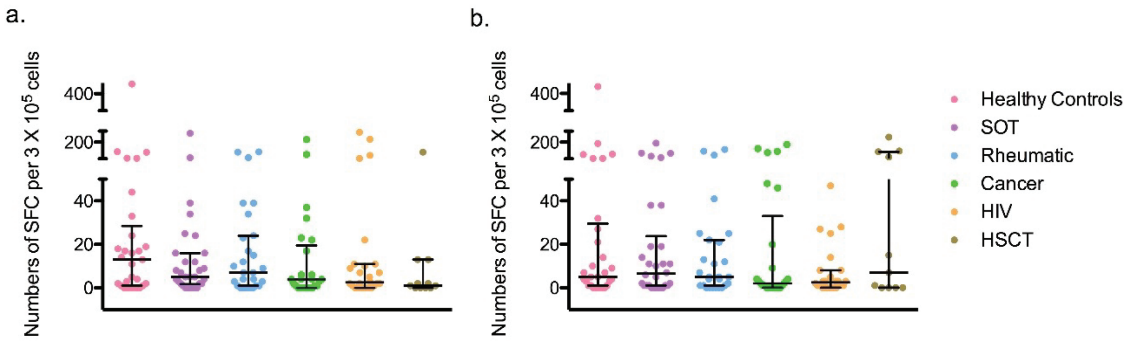

Figure 3. Quantification of interferon γ–secreting spot-forming cells (SFCs) in healthy controls and immunosuppressed patients after vaccination with CoronaVac. Peripheral blood mononuclear cells (PBMCs; 3×10^5 cells) were obtained 8–12 weeks after a second dose of CoronaVac from heathy controls (n = 29) and the following immunosuppressed patient groups: solid organ transplant (SOT) (n = 30), cancer (n = 25), rheumatic diseases (n = 27), human immunodeficiency virus infected (HIV+) (n = 26), and hematopoietic stem cell transplant (HSCT) (n = 11). PBMCs were stimulated with 15-mer peptides (megapool peptides derived from the spike and the remaining proteins [MP-S + MP-R]) (*A*) or 8–9-mer peptides (CD8A + CD8B) (*B*) from severe acute respiratory syndrome coronavirus 2 proteins. SFCs were quantified using an enzyme-linked immunospot assay and are displayed as medians with interquartile ranges.

infection and worse outcomes compared with persons without immune dysfunction, with up to 27% of vaccinated SOT recipients requiring hospitalization, >10% required admission to the intensive care unit, and >5% dying [17, 22, 23].

Oncological patients have also been reported to be at high risk of severe COVID-19, with an estimated fatality rate of 25.6% versus 2.7% in the general population [24]. Studies in patients undergoing chemotherapy show reduced immunogenicity after 2 doses of the BNT162b2 mRNA vaccine [25]. Our study shows that cancer patients with solid tumors receiving chemotherapy, despite having a comparable TAb response, attain a lower neutralizing capacity than the control group with this vaccine. Conversely, in HSCT recipients, humoral response did not differ from that in controls, although the low number of participants and heterogeneity in underlying disease and type of transplant in this group may prevent definite conclusions.

Immune function in people living with HIV (PLHIV) is impaired owing to depletion of the CD4 T cells, and dysfunction of cellular and humoral immunity leads to weakening vaccine response [26]. SARS-CoV-2 vaccine response in PLHIV has been scarcely assessed, with no study reporting so far on inactivated vaccines to our knowledge. Two studies found that the ChAdOx1 nCoV-19 vaccine elicits similar humoral and cell-mediated immune responses as in healthy individuals [27, 28]. Subsequently, PLHIV vaccinated with mRNA-1273 or BNT162b2 exhibited robust immune responses comparable to those in healthy individuals [29]. In contrast, our findings indicate that humoral response to this inactivated SARS-CoV-2 vaccine in PLHIV is significantly impaired, which may reflect the fact that we included only participants with CD4 cell counts ≤500/μL.

In inflammatory arthritis, both the disease and biologic immunomodulators used in its treatment can affect cellular and humoral immunity [30]. We found a significantly weaker humoral response in patients with autoimmune rheumatic diseases treated with biologic agents. An impairment in humoral response has also been described with BNT162b2 vaccine in other autoimmune rheumatic diseases, associated with older age and the use of methotrexate, steroids, mycophenolate, abatacept, and rituximab [31, 32]. A 2021 meta-analysis involving various autoimmune inflammatory diseases found >90% seroconversion rates for mRNA vaccines in patients receiving anti-TNF, but combinations of anti-TNF with immunomodulators resulted in an attenuated vaccine response compared with anti-TNF monotherapy [33]. CoronaVac was evaluated in patients with rheumatic diseases in 2 studies conducted in Brazil. In the first study, patients with immune-mediated diseases were less likely than healthy controls to have detectable anti–S1 IgG (TAb) [34], whereas in the second, lower rates of TAb seroconversion (70.4% vs 95.5%;) and NAb positivity (56.3% vs 79.3%; both $P < .001$) were detected 6 weeks after vaccination in the autoimmune rheumatic diseases group, compared with the control group [35].

The development of vaccines to prevent SARS-CoV-2 infection has mainly relied on the induction of NAb to the spike protein of SARS-CoV-2, but there is growing evidence that T-cell immune response can contribute to protection as well. We know that mRNA vaccines elicit spike protein–targeted T-cell responses, intracellular cytokine staining, and cytokine profile [36]. We observed no differences when each subgroup was compared with the control group. These results could be explained either by the reduced number of patients or by the fact that CoronaVac can still promote, to some extent, the expansion of IFN-γ–secreting T cells in immunocompromised persons.

The present study suggests that the current schedule with 2 doses of CoronaVac is insufficient to induce an acceptable immune response in immunocompromised persons; thus,

booster dosing or primary vaccination with >2 doses is needed. Multiple vaccine doses can boost the primary immune response by providing supplementary innate immune activation signals and promoting further expansion of previously activated T- and B-cell clones [37]. A third dose in immunocompromised patients is already being recommended in France, Israel, Chile, United States, and several other countries. A study has shown significant improvement in immunogenicity after administration of a third dose of the BNT162b2 vaccine to SOT recipients [38]. However, another study reported that 51% of the kidney transplant recipients who did not respond after 2 doses of mRNA-1273 vaccine did not develop anti–SARS-CoV-2 antibodies after the third dose, especially those receiving triple immunosuppression [39]. Multiple-dose strategies must be followed up with long-term effectiveness and immunogenicity studies.

Our study had some limitations. First, we did not evaluate the prevalence of anti–SARS-CoV-2 antibodies before vaccination. However, we excluded participants reporting a previous positive SARS-CoV-2 reverse-transcription quantitative polymerase chain reaction, specific antibodies, or a clinical history of COVID-19. Second, we did not attain the prespecified sample size, given the strict enrollment period and that all participants had been vaccinated in a national program and within a very short period of time. However, the differences in humoral response between the immunocompromised and control groups were higher than expected, which allowed reducing the number needed to demonstrate significance. Furthermore, adjustment for other relevant covariates, such as age, did not modify the findings. Third, we did not evaluate immune response to other relevant SARS-CoV-2 variants, such as Delta. However, our previous data in immunocompetent persons showed that levels of NAbs against Delta were equivalent to the levels reached for the Gamma variant with CoronaVac vaccine [40].

Strengths of our study include the inclusion of an immunocompetent control group and assessment of both full humoral and memory T-cell responses. In addition, this is the first study to report the response to 2 doses of CoronaVac inactivated SARS-CoV-2 vaccine in PLHIV and SOT.

Finally, systematic assessing of immune response in all vaccine recipients to verify immunogenicity status is currently not recommended because no validated biomarkers for both humoral and cellular immunity are correlated with protection, as suggested by previous analyses of the immune response of CoronaVac breakthrough cases in immunocompetent adults [41]. In the current study, we observed that a substantial proportion of immunocompromised recipients have no detectable NAb at all and probably remain at a high risk for COVID-19 even after vaccination. Our results fully support the necessity of additional vaccine doses in primary vaccination schemes in the immunocompromised population.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. World Health Organization. Weekly epidemiological update on COVID-19—27 July 2021. Available at: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---27-july-2021. Accessed 18 September 2021.
2. He Q, Mao Q, Zhang J, et al. COVID-19 vaccines: current understanding on immunogenicity, safety, and further considerations. Front Immunol **2021**; 12.
3. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med **2020**; 383:2603–15.
4. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med **2020**; 384:403–16.
5. Choi EM. COVID-19 vaccines for low- and middle-income countries. Trans R Soc Trop Med Hyg **2021**; 115:447–56.
6. Lim WW, Mak L, Leung GM, Cowling BJ, Peiris M. Comparative immunogenicity of mRNA and inactivated vaccines against COVID-19. Lancet Microbe **2021**; 8:e423.
7. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med **2021**; 27:1205–11.
8. Cromer D, Steain M, Reynaldi A, et al. Neutralising antibody titres as predictors of protection against SARS-CoV-2 variants and the impact of boosting: a meta-analysis. Lancet Microbe **2022**; 3:e52–61.
9. Ministerio de Salud (Chile). Plan nacional de vacunacion COVID 2021. Available at: https://www.gob.cl/yomevacuno/#vacunados. Accessed 18 September 2021.
10. Tanriover MD, Doğanay HL, Akova M, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet **2021**; 398:213–22.
11. Jara A, Undurraga EA, González C, et al. Effectiveness of an inactivated SARS-CoV-2 Vaccine in Chile. N Engl J Med **2021**; 10:875–84.
12. Tan CW, Chia WN, Qin X, et al. A SARS-CoV-2 surrogate virus neutralization test based on antibody-mediated blockage of ACE2–spike protein–protein interaction. Nat Biotechnol **2020**; 38:1073–8.
13. Bueno SM, Abarca K, González PA, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine in a subgroup of healthy adults in Chile. Clin Infect Dis **2021**.
14. Grifoni A, Weiskopf D, Ramirez SI, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. Cell **2020**; 181:1489–1501.e15.
15. Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis **2021**; 21:181–92.
16. Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, et al. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully-vaccinated hospitalized COVID-19 patients in Israel. Clin Microbiol Infect **2021**; 11:L1652–7.
17. Sun J, Zheng Q, Madhira V, et al. Association between immune dysfunction and COVID-19 breakthrough infection after SARS-CoV-2 vaccination in the US. JAMA Intern Med **2021**; 2:153–62.
18. Marion O, Del Bello A, Abravanel F, et al. Safety and immunogenicity of anti-SARS-CoV-2 messenger RNA vaccines in recipients of solid organ transplants. Ann Intern Med **2021**; 9:1336–8.
19. Narasimhan M, Mahimainathan L, Clark AE, et al. Serological response in lung transplant recipients after two doses of SARS-CoV-2 mRNA vaccines. Vaccines (Basel) **2021**; 9.
20. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. JAMA **2021**; 325:2204–6.
21. Schramm R, Costard-Jäckle A, Rivinius R, et al. Poor humoral and T-cell response to two-dose SARS-CoV-2 messenger RNA vaccine BNT162b2 in cardiothoracic transplant recipients. Clin Res Cardiol **2021**; 1:8.
22. Reischig T, Kacer M, Vlas T, et al. Insufficient response to mRNA SARS-CoV-2 vaccine and high incidence of severe COVID-19 in kidney transplant recipients during pandemic. Am J Transplant **2021**; 3:801–12.
23. Caillard S, Chavarot N, Bertrand D, et al. Occurrence of severe COVID-19 in vaccinated transplant patients. Kidney Int **2021**; 100:477–9.
24. Saini KS, Tagliamento M, Lambertini M, et al. Mortality in patients with cancer and coronavirus disease 2019: a systematic review and pooled analysis of 52 studies. Eur J Cancer **2020**; 139:43–50.
25. Massarweh A, Eliakim-Raz N, Stemmer A, et al. Evaluation of seropositivity following BNT162b2 messenger RNA Vaccination for SARS-CoV-2 in patients undergoing treatment for cancer. JAMA Oncol **2021**; 8:1133–40.
26. El Chaer F, El Sahly HM. Vaccination in the adult patient infected with HIV: a review of vaccine efficacy and immunogenicity. Am J Med **2019**; 132:437–46.
27. Frater J, Ewer KJ, Ogbe A, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 in HIV infection: a single-arm substudy of a phase 2/3 clinical trial. Lancet HIV **2021**; 8:474–85.
28. Madhi SA, Baillie V, Cutland CL, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 vaccine against the B.1.351 variant. N Engl J Med **2021**; 384r:1885–98.
29. Woldemeskel BA, Karaba AH, Garliss CC, et al. The BNT162b2 mRNA vaccine elicits robust humoral and cellular immune responses in people living with HIV. Clin Infect Dis **2021**; 74:1268–70. doi: 10.1093/cid/ciab648
30. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. Rheumatology (Oxford) **2013**; 52:53–61.
31. Mahil SK, Bechman K, Raharja A, et al. The effect of methotrexate and targeted immunosuppression on humoral and cellular immune responses to the COVID-19 vaccine BNT162b2: a cohort study. Lancet Rheumatol **2021**; 3:627–37.
32. Braun-Moscovici Y, Kaplan M, Braun M, et al. Disease activity and humoral response in patients with inflammatory rheumatic diseases after two doses of the Pfizer mRNA vaccine against SARS-CoV-2. Ann Rheum Dis **2021**; 10:1317–21.
33. Jena A, Mishra S, Deepak P, et al. Response to SARS-CoV-2 vaccination in immune mediated inflammatory diseases: systematic review and meta-analysis. Autoimmun Rev **2022**; 21:102927.
34. Seyahi E, Bakhdiyarli G, Oztas M, et al. Antibody response to inactivated COVID-19 vaccine (CoronaVac) in immune-mediated diseases: a controlled study among hospital workers and elderly. Rheumatol Int **2021**; 41:1429–40.
35. Medeiros-Ribeiro AC, Aikawa NE, Saad CGS, et al. Immunogenicity and safety of the CoronaVac inactivated vaccine in patients with autoimmune rheumatic diseases: a phase 4 trial. Nat Med **2021**; 10:1744–51.
36. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature **2020**; 586:594–9.
37. Heeger PS, Larsen CP, Segev DL. Implications of defective immune responses in SARS-CoV-2 vaccinated organ transplant recipients. Sci Immunol **2021**; 6:eabj6513.
38. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. N Engl J Med **2021**; 385:661–2.
39. Benotmane I, Gautier G, Perrin P, et al. Antibody response after a third dose of the mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients with minimal serologic response to 2 doses. JAMA **2021**; 11:1063–5.
40. Melo-González F, Soto JA, González LA, et al. Recognition of variants of concern by antibodies and T cells induced by a SARS-CoV-2 inactivated vaccine. Front Immunol **2021**; 12.
41. Duarte LF, Gálvez NMS, Iturriaga C, et al. Immune profile and clinical outcome of breakthrough cases after vaccination with an inactivated SARS-CoV-2 vaccine. Front Immunol **2021**; 12:742914.