Safety and immunogenicity of COVID-19 vaccination in immunocompromised patients

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic poses a great threat to public health. Individuals who are immunocompromised because of the progression of the primary disease or receiving immunosuppressive medications are prone to severe COVID-19 complications and poor outcomes. Abundant data have shown that many COVID-19 vaccines are safe and effective in large-scale populations; however, these clinical trials have excluded immunocompromised populations. Available evidence indicates that immunocompromised populations have a blunted immune response to other vaccines, raising concerns regarding the efficacy of COVID-19 vaccination in these populations. Thus, there is an urgent need to delineate the efficacy of COVID-19 vaccines in these vulnerable populations. Here, we review the characteristics of specific humoral and cellular responses to COVID-19 vaccination in immunocompromised populations, including HIV-infected patients and those receiving immunosuppressive treatment, especially solid organ transplant recipients and those undergoing anti-CD20 treatment. We also addressed the challenges that immunocompromised populations will face in the future pandemic and the need for basic and clinical translational studies to highlight the best vaccination strategies for these populations.

Keywords: Anti-CD20 treatment; Coronavirus disease 2019; Human immunodeficiency virus; Immunocompromised; Solid organ transplant recipient; Vaccine

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for coronavirus disease 2019 (COVID-19), has had a global impact since its discovery. As of August 25, 2022, >595 million confirmed cases of COVID-19 and 6.4 million deaths have been reported worldwide (https://covid19.who.int/). Historically, vaccines have been the most powerful weapon to fight infectious diseases. The early and timely submission of the virus sequence to the World Health Organization (WHO) by the Chinese government significantly promoted the development of the COVID-19 vaccine.[1] Abundant data have shown that the COVID-19 vaccines developed by different research platforms are safe and effective for large-scale populations.[2-6] However, immunocompromised populations who had a higher risk of COVID-19-related hospitalization, severe disease, or death[7] were excluded from large clinical trials. Thus, the efficacy of these COVID-19 vaccines in immunocompromised patients requires urgent clarification.

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Immunocompromised conditions are usually observed in those with primary or secondary immunodeficiency caused by the progression of a disease or patients receiving immunosuppressive treatment. A lower vaccination response rate, such as that observed for the influenza vaccination, is commonly observed in immunocompromised populations.[8] Among the secondary immunodeficiencies, human immunodeficiency virus (HIV) infection represents the classical immunocompromised state caused by the disease progression. HIV mainly infects $CD4^+$ T cells and leads to their death by apoptosis or pyroptosis.[9] Without antiretroviral therapy (ART), HIV destroys the immune system and leads to the progression of acquired immunodeficiency syndrome (AIDS). Among the patients with secondary immunodeficiency conditions caused by immunosuppressive medications, the immune response to the COVID-19 vaccine was reported to be the lowest in solid organ transplantation recipients (SOTRs) and those receiving anti-CD20 B cell-depleting treatment [Figure 1]. Thus, we mainly focused on these two populations

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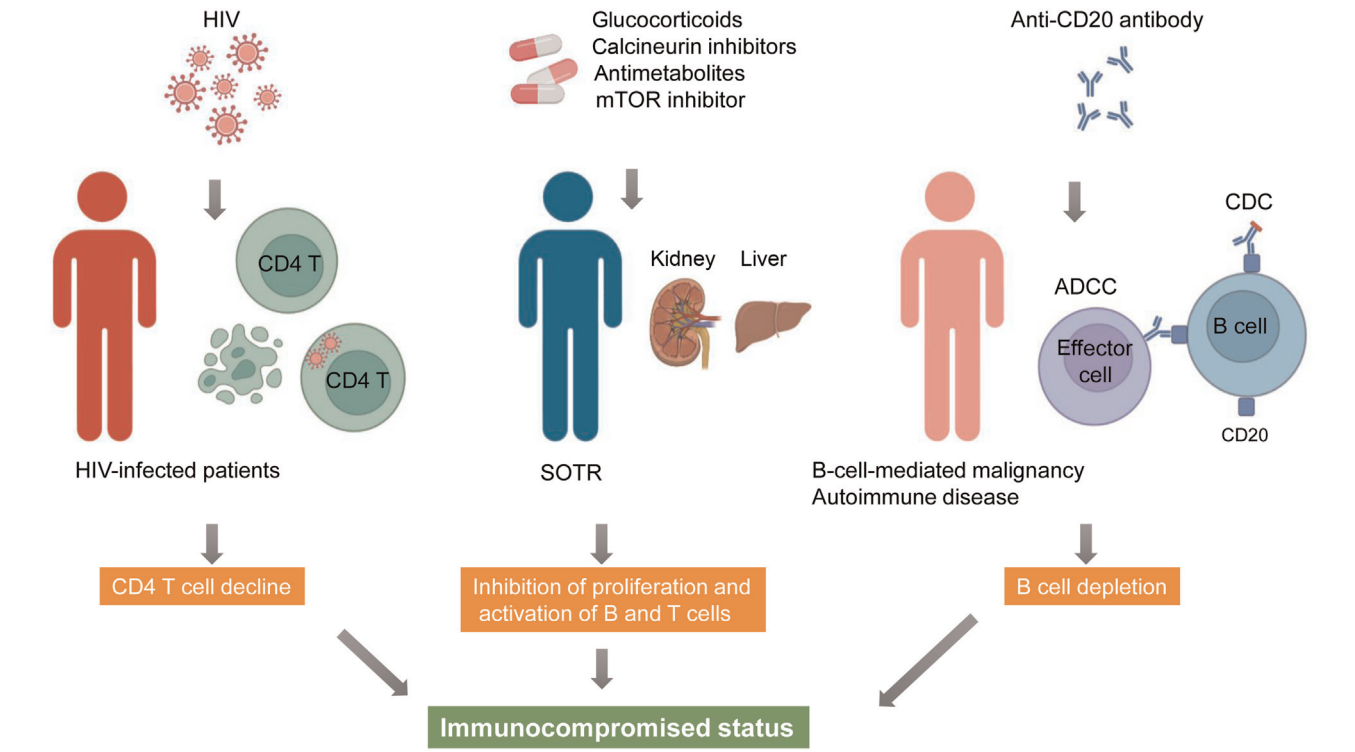

Figure 1: Model for three immunocompromised conditions in this study. ADCC: Antibody-dependent cell-mediated cytotoxicity; CD: Cluster of differentiation; CDC: Complement-dependent cytotoxicity; HIV: Human immunodeficiency virus; mTOR: Mammalian target of rapamycin; SOTR: Solid organ transplantation recipient. This illustration was created using biorender.com.

receiving immunosuppressive treatments. Most of the SOTRs need to receive immunosuppressive drugs to prevent graft rejection, including glucocorticoids, calcineurin inhibitors (CNI), antimetabolites, and mammalian target of rapamycin inhibitors.[10] These immunosuppressive drugs may block the activation or proliferation of B and T lymphocytes, leading to a poor immune response to the COVID-19 vaccine. Anti-CD20 treatment is mainly used to treat B cell-mediated malignancies and various autoimmune disorders (eg, rheumatoid arthritis and multiple sclerosis).[11] However, treatment with anti-CD20 leads to non-specific and overall suppression of humoral immunity. Thus, the immune response to COVID-19 vaccination in patients receiving CD20 monoclonal antibodies was significantly impaired. Identifying the underlying risk factors for poor immune response to COVID-19 vaccination will aid in improving vaccination strategies for these vulnerable populations.

In this review, we focus on the immunogenicity of different types of COVID-19 vaccines in immunocompromised populations, particularly HIV-infected individuals, SOTRs, and anti-CD20 recipients.

COVID-19 Vaccines

Types of COVID-19 vaccines

As of July 2022, the WHO has reported that there are 359 COVID-19 vaccine candidates being evaluated. Among them, 161 are in the clinical phase and 198 in the preclinical phase, including 39 candidates being or having been detected in phase III clinical trials and 11 candidates being or having been detected in phase IV clinical trials (https://www.who.int/teams/blueprint/covid-19/covid-19-vaccine-tracker-and-landscape).

COVID-19 vaccine coverage

Notably, 11 vaccines have been authorized by the WHO for emergency use [Table 1]. According to the production platforms, these vaccines can be mainly divided into the following four categories: (1) inactivated vaccines: inactivated whole SARS-CoV-2 virions were used to trigger an immune response with highly accepted safety; (2) recombinant protein vaccines: the simulated protein fragment or shell of the SARS-CoV-2 virion was used to trigger an immune response with the help of adjuvant; (3) virus vector vaccines: viral vectors that transfect the gene encoding SARS-CoV-2 proteins were used to trigger an immune response; (4) messenger ribonucleic acid (mRNA) vaccines: the genetically modified mRNA sequence of SARS-CoV-2 protein was used to trigger an immune response. Compared with other technologically traditional vaccines, mRNA vaccines can induce much stronger humoral responses and are more widely used worldwide.[12,13] Although inactivated-virus vaccines are mostly used in China to vaccinate residents, more than six domestic mRNA vaccines are being developed. For example, ArCoV produced by Abogen Biosciences is being examined in phase III clinical trials and might be used in COVID-19 vaccination programs.[14]

As of September 2022, approximately 67.7% of the global population is vaccinated with more than one dose of

Table 1: COVID-19 vaccines as emergency use issued by the WHO.

Candidate vaccine	Vaccine platform description	Developer	Number of doses	Schedule	Route of administration	Storage temperature	Number of approved countries	Potential serious side effects
mRNA-1273 (Spikevax)	mRNA	Moderna	2	Day 0 + 28	Intramuscular	2–8°C for 30 days, −20°C for 6 months	88	Myocarditis and pericarditis
BNT162b2 (Comirnaty)	mRNA	Pfizer/BioNTech	2	Day 0 + 21	Intramuscular	−70°C	148	–
COVOVAX (Novavax formulation)	Protein subunit	Serum Institute of India	2	Day 0 + 21	Intramuscular	2–8°C	5	–
Nuvaxovid	Protein subunit	Novavax	2	Day 0 + 21	Intramuscular	2–8°C	39	–
Ad5-nCov (Convidecia)	Replication-defective adenovirus type 5 vector	CanSino	2	Day 0 + 21	Intramuscular	2–8°C	10	Thrombotic thrombocytopenia syndrome
Ad26.COV2.S	Replication-incompetent human adenovirus type 26 vector	Janssen (Johnson & Johnson)	1–2	Day 0 or Day 0 + 56	Intramuscular	2–8°C	113	Thrombotic thrombocytopenia syndrome and Guillain-Barré syndrome
AZD1222 (Vaxzevria)	Replication-defective chimpanzee adenovirus vector	Oxford/AstraZeneca	1–2	Day 0 or Day 0 + 28	Intramuscular	2–8°C	148	Thrombotic thrombocytopenia syndrome and Guillain-Barré syndrome
Covishield	Replication-defective chimpanzee adenovirus vector	Serum Institute of India	1–2	Day 0 or Day 0 + 28	Intramuscular	2–8°C	49	Thrombotic thrombocytopenia syndrome and Guillain-Barré syndrome
Covaxin	Inactivated	Bharat Biotech	2	Day 0 + 14	Intramuscular	2–8°C	14	–
BBIBP-CorV (Covilo)	Inactivated	Sinopharm (Beijing)	2	Day 0 + 21	Intramuscular	2–8°C	93	–
CoronaVac	Inactivated	Sinovac	2	Day 0 + 14	Intramuscular	2–8°C	56	–

COVID-19: Coronavirus disease 2019; mRNA: Messenger ribonucleic acid; WHO: World Health Organization. https://covid19.trackvaccines.org/agency/who/.

COVID-19 vaccine (https://covid19.who.int/). In China, inactivated-virus vaccines are primarily used; >90.5% of the population has completed primary vaccination, and 71.7% of the population has received a booster vaccination. In high-income countries, mRNA vaccines or adenovirus vector vaccines are primarily used; approximately 79.8% of the population receives more than one dose of the COVID-19 vaccine, 74.9% of the population completed primary vaccination, and 44.8% of the population received a booster vaccination (https://app.powerbi.com/). However, in low-income countries, only 53.2% of the population has received more than one dose of the COVID-19 vaccine, 37.5% of the population has completed primary vaccination, and 9.8% of the population has received a booster vaccination. An imbalance in accessing COVID-19 vaccines is particularly noteworthy in Africa. Owing to underdeveloped technology in Africa, the COVID-19 vaccines can rarely be domestically produced, and the population mainly relies on international support. Hence, Africa has the lowest vaccination rate worldwide, and this has been proven to be dangerous. Extreme vaccine inequities and low vaccination rates pose a great threat to immunocompromised patients.

Safety of COVID-19 vaccine

The safety of COVID-19 vaccines has been thoroughly and rigorously assessed in the general population. Serious side effects were infrequently reported after COVID-19 vaccination, such as thrombotic thrombocytopenia syndrome and Guillain-Barré Syndrome for several virus vector vaccines, and myocarditis and pericarditis for mRNA vaccine, mRNA-1273 [Table 1]. Generally, COVID-19 vaccinations in immunocompromised patients are safe. The side effects after COVID-19 vaccination are mild and temporary. Similar rate of side effects and no additional adverse effects of the COVID-19 vaccines have been reported in immunocompromised patients. Thus, we mainly focus on the immunogenicity of COVID-19 vaccines in the following sections.

Immunogenicity of the COVID-19 Vaccine in Specific Immunocompromised Populations

HIV-infected patients

HIV infection remains a global public health issue, with an estimated 38 million people living with HIV. In untreated patients, the CD4 T cell count declines continuously and eventually progresses to the AIDS stage, in which the immune system is severely weakened. Multiple large cohort studies have shown that HIV-infected patients, especially those with low CD4 T cell count and unsuppressed viremia, experience more severe COVID-19 and poorer clinical outcomes than those without HIV.[15-20] Thus, HIV-infected patients, particularly those with immunosuppression, should be prioritized to receive the COVID-19 vaccine to reduce the risk of COVID-19.

The immunogenicity of COVID-19 vaccines in HIV-infected individuals has been reported inconsistently. Some studies found poorer immunogenicity to the COVID-19 vaccine in HIV-infected individuals compared

with healthy controls (HCs), but other studies showed comparable immunogenicity between these two groups. This discrepancy may be due to the different numbers of enrolled participants, the different methods used to monitor the humoral response, or the heterogeneity, including age, ethnicity, CD4 T cell count, etc., of the enrolled HIV-infected population. Many clinical trials are still ongoing to fully elucidate the immunogenicity of the COVID-19 vaccination in HIV-infected patients [Supplementary Table 1, http://links.lww.com/CM9/B381]. Here, we also summarized the humoral immune responses to the COVID-19 vaccine in HIV-infected patients in Table 2, and only studies that enrolled >50 HIV-infected patients were included. Accumulating evidence from large cohort studies has revealed worse immunogenicity of COVID-19 vaccines in HIV-infected patients, especially those with low CD4 T cell counts and unsuppressed viral loads. A study conducted in Brazil revealed that HIV-infected patients mount reduced immunogenicity compared with HCs after receiving two doses of inactivated CoronaVac vaccine, and HIV-infected patients with CD4 counts <500 cells/μL had lower immunogenicity than those patients with a CD4 count of at least 500 cells/μL.[21] In addition, 71% of HIV-infected patients were neutralizing antibody (NAb)-positive compared with 84% of HCs.[21] A study by Spinelli *et al*[22] reported that following COVID-19 mRNA vaccination, HIV-infected patients had a lower surrogate virus neutralization test response, particularly among those with lower CD4 T cell counts. Similarly, a study conducted in Switzerland also reported a lower titer of anti-receptor binding domain (RBD) antibody after SARS-CoV-2 mRNA vaccination in HIV-infected patients compared with that in healthy volunteers.[23] In addition, a recent study conducted by Madhi *et al*[24] showed that HIV-infected patients had attenuated immunoglobulin G (IgG) antibody against spike protein (anti-spike IgG) titers after receiving two doses of recombinant spike protein nanoparticle vaccine NVX-CoV2373 compared with their healthy counterparts, while the seroconversion rate was similar. Some real-world studies also found reduced RBD-IgG, Spike-IgG, or seropositivity in HIV-infected patients compared with HCs, and the antibody response is particularly poor in HIV-infected patients with CD4 T cell counts <200 cells/μL.[25,26] However, some studies reported similar immunogenicity induced by COVID-19 vaccination. For example, a study conducted by Madhi *et al*[27] evaluated the humoral response after receiving an adenovirus-vectored vaccine AZD1222 in HIV-infected patients, and they found similar RBD-IgG and NAb responses between HIV-infected patients and HIV-negative participants. In the era of ART, most HIV-infected patients have received ART treatment. However, there are still some patients who have not received ART and some studies have shown poor humoral response to the COVID-19 vaccine in HIV-infected patients with unsuppressed viremia.[22,28] Compared with the widely examined humoral response, antigen-specific T cell responses have only been detected in a few studies. Woldemeskel *et al*[29] evaluated cellular immunity using interferon gamma (IFN-γ) ELISpot assay in 12 HIV-infected patients following two doses of BNT162b2 mRNA vaccine and found no difference in cellular immunity between HIV-infected patients and HCs. Compared with HIV-negative individuals, no difference in cellular responses was observed in 54 HIV-infected patients receiving two doses of ChAdOx1 nCoV-19.[30] However, the immune status of the enrolled HIV-infected patients may have affected the cellular immune response. A case study revealed failed seroconvert and undetectable spike-specific T cells in one patient with advanced HIV infection (CD4 T-cell count: 20 cells/μL, viral load: 831,764 copies/mL).[28]

Collectively, well-treated HIV-infected patients with immune status comparable to healthy individuals may exhibit a similar immune response to the COVID-19 vaccine compared with healthy individuals. However, some HIV-infected patient, especially those in immunosuppressed conditions with poor CD4 T cell counts and unsuppressed viremia, might mount an attenuated immune response to the COVID-19 vaccine.

SOTRs with immunosuppressive medication

SOTRs with kidney, liver, or lung transplants are at increased risk of severe SARS-CoV-2 infection or COVID-19-related mortality.[43-45] Immunosuppression in SOTRs is mainly due to the use of immunosuppressive medications aiming at preventing allograft rejection. The use of immunosuppressive drugs might block the cellular and humoral immune responses and result in a poor vaccine response, which has been observed in SOTRs receiving other vaccine (influenza, hepatitis B vaccine, etc.). For example, CNI (tacrolimus or cyclosporin) can block the activation of T cells, and mycophenolate mofetil (MMF) can inhibit the proliferation of T and B cells.

Although SOTRs were excluded from large COVID-19 vaccine clinical trials, vaccination of SOTRs has been suggested by professional societies. Larger cohort studies have consistently concluded that both antibody positivity and titers are extremely low in SOTRs after receiving the COVID-19 vaccine [Table 3].[46-60] Boyarsky *et al*[61] found that anti-spike IgG was only detectable in 54% (357/658) of SOTRs after two doses of SARS-CoV-2 mRNA vaccine. Bertrand *et al*[62] evaluated the anti-spike antibody in 225 kidney transplant recipients (KTRs) after two doses of the BNT162b2 vaccine, and only 8 KTRs (17.8%) developed SARS-CoV-2 antibodies. One study conducted by Rabinowich *et al*[55] evaluated 80 liver transplant recipients (LTRs) after two doses of BNT162b2 vaccination, of whom only 47.5% were positive for SARS-CoV-2 IgG antibodies, and the antibody titer was also reduced in LTRs. Havlin *et al*[63] reported that none of the lung transplant recipients developed SARS-CoV-2 IgG after the first and second doses of BNT162b2 vaccine. In addition, studies comparing the immunogenicity of COVID-19 vaccines in immunocompromised patients also identified SOTRs as the least likely to achieve seroconversion after COVID-19 vaccination.[36,64,65] Older age, shorter time from transplantation, high-dose of steroids, receiving triple immunosuppression regimen, regimens including MMF, and co-morbidities including diabetes and hypertension were identified as the risk factors for compromised humoral response.[47,50,51,55,57,66] In addition, impaired SARS-CoV-2-specific T cell responses have been reported in

Table 2: Summary of studies on humoral immune response to COVID-19 vaccination in HIV-infected patients compared with HCs.

Reference	Journal	Vaccine	Numbers (PLWH *vs.* HC)	PLWH grouped based on CD4 T cell counts (cells/mL)	Detection time points after full course vaccination	Detected parameters	Findings
Liu *et al*[31]	*Vaccines*	CoronaVac	55 *vs.* 21	CD4 < 350 CD4 ≥ 350	5 weeks	Anti-RBD IgG	Similar between PLWH and HC, but lower in PLWH with CD4 counts <350 cells/μL
Ao *et al*[32]	*Emerg Microbes Infect*	CoronaVac or BBIBP-CorV	139 *vs.* 120	CD4 < 200 200 ≤ CD4 ≤ 500 CD4 > 500	40 days	Anti-RBD IgG Anti-spike IgG	Lower in PLWH, especially in those with CD4 counts <200 cells/μL Lower titers in PLWH
Cai *et al*[33]	*J Med Virol*	CoronaVac or BBIBP-CorV	143 *vs.* 50	NA	35.78 days	SARS-CoV-2 IgG NAb	Lower in PLWH Similar
Netto *et al*[21]	*Lancet HIV*	CoronaVac	215 *vs.* 296	CD4 < 500 CD4 ≥ 500	6 weeks	Anti-spike IgG NAb	Lower in PLWH, and lower seroconversion in those with CD4 counts <500 cells/μL Lower in PLWH, especially in those with CD4 counts <500 cells/μL
Huang *et al*[34]	*Viruses*	CoronaVac or BBIBP-CorV	94 *vs.* 51	NA	NA	Anti-spike IgG NAb	Lower in PLWH Similar
Zeng *et al*[35]	*Vaccines*	BBIBP-CorV CoronaVac	65 *vs.* 65 67 *vs.* 65	CD4 < 350 CD4 ≥ 350	28 days	Anti-RBD IgG	Lower in PLWH, especially in those with CD4 counts <350 cells/μL
Bergman *et al*[36]	*EBioMedicine*	BNT162b2	90 *vs.* 90	CD4 > 300 CD4 ≤ 300	14 days	Anti-RBD IgG	Similar
Jedicke *et al*[37]	*HIV Med*	BNT162b2	50 *vs.* 41	NA	35 days	Anti-spike IgG	Lower in PLWH
Levy *et al*[38]	*Clin Microbiol Infect*	BNT162b2	143 *vs.* 261	NA	18 days	Anti-RBD IgG NAb	Lower in PLWH Similar
Portillo *et al*[23]	*Front Immunol*	BNT162b2 or mRNA-1273	124 *vs.* 48	NA	30 days	Anti-RBD IgG	Lower in PLWH
Spinelli *et al*[22]	*Clin Infect Dis*	BNT162b2 or mRNA-1273	100 *vs.* 100	NA	35 days	SARS-CoV-2 IgG NAb	Lower in PLWH Lower in PLWH
Antinori *et al*[39]	*Clin Infect Dis*	BNT162b2 or mRNA-1273	166 *vs.* 169	CD4 < 200 200 ≤ CD4 ≤ 500 CD4 > 500	1 month	Anti-RBD IgG NAb	Lower in PLWH, especially in those with CD4 counts <200 cells/μL Lower in PLWH, especially in those with CD4 counts <200 cells/μL
Heftdal *et al*[40]	*J Intern Med*	BNT162b2	269 *vs.* 538	NA	>1 week	Anti-RBD IgG NAb	Lower in PLWH Similar
Lombardi *et al*[41]	*Lancet Reg Health Eur*	mRNA-1273	62 *vs.* 8	CD4 < 350 350 ≥ CD4 ≤ 500 CD4 > 500	28 days	Anti-spike IgG NAb	Similar Similar
Tau *et al*[42]	*Open Forum Infect Dis*	BNT162b2	136 *vs.* 61	CD4 < 300 CD4 ≥ 300	4.5 months	Anti-RBD IgG	Similar between PLWH and HC, but lower in PLWH with CD4 counts <300 cells/μL
Madhi *et al*[24]	*Lancet HIV*	NVX-CoV2373	58 *vs.* 1216	NA	14 days	Anti-spike IgG NAb	Lower in PLWH Lower in PLWH

Anti-RBD IgG: IgG antibody against receptor-binding domain; Anti-spike IgG: IgG antibody against spike protein; CD4: Cluster of differentiation 4; COVID-19: Coronavirus disease 2019; HC: Healthy control; HIV: Human immunodeficiency virus; IgG: Immunoglobulin; NA: Not applicable; NAb: Neutralizing antibody; PLWH: People living with HIV; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Table 3: Summary of studies on humoral immune response to COVID-19 vaccination in SOTRs compared with HCs.

Reference	Journal	Vaccines	Study population (*n*)	Detection time points after full course vaccination	Detected parameters (positivity)	Factors associated with worse humoral response
Benotmane *et al*[46]	*Kidney Int*	mRNA-1273	KTR (205)	1 month	SARS-CoV-2 IgG (48%)	Treatment with CNI, MMF, or steroids
Cucchiari *et al*[47]	*Am J Transplant*	mRNA-1273	KTR (148)	2 weeks	Anti-spike IgM/IgG (29.9%)	Diabetes, treatment with ATG during the last year
Devresse *et al*[48]	*Transplantation*	BNT162b2	KTR (90)	1 month	Anti-RBD IgG (64.4%)	NA
Eren Sadioglu *et al*[49]	*Transpl Infect Dis*	CoronaVac	KTR (118)	1 month	Anti-SARS-CoV-2 IgG (18.8%)	Age and impaired renal function
Grupper *et al*[50]	*Am J Transplant*	BNT162b2	KTR (136)	16.5 days	Anti-SARS-CoV-2 IgG (37.5%)	Age, high-dose corticosteroids, and triple immunosuppression regimen including MMF
Guarino *et al*[51]	*J Hepatol*	BNT162b2	LTR (365)	4 weeks	Anti-spike IgG (74.8%)	Age, higher BMI, shorter time from transplantation, multiple immunosuppressive drugs, and antimetabolite therapy
Hallett *et al*[52]	*J Heart Lung Transplant*	BNT162b2 or mRNA-1273	HTR (134) Lung transplant recipient (103)	28 days	Anti-spike IgG (62% and 36%, respectively)	Antimetabolite regimen, shorter years (<6 years) from transplantation
Hod *et al*[53]	*Transplantation*	BNT162b2	KTR (120)	26.7 days	Anti-RBD IgG (43.4%) NAb (35%)	MPA dose and hemoglobin level <13 g/dL
Midtvedt *et al*[54]	*Transplantation*	BNT162b2	KTR (141)	25–89 days	Anti-spike IgG (18%)	Age, treatment with MPA, especially in triple therapy
Rabinowich *et al*[55]	*J Hepatol*	BNT162b2	LTR (80)	14.8 days	Anti-spike IgG (47.5%)	Age, decreased renal function, and immunosuppression
Rozen-Zvi *et al*[56]	*Clin Microbiol Infect*	BNT162b2	KTR (308)	2–4 weeks	Anti-spike IgG (36.4%)	Age, lower eGFR, high MPA dose, and higher CNI blood level
Ruether *et al*[57]	*Clin Gastroenterol Hepatol*	BNT162b2 or mRNA-1273 or AZD1222	LTR (141)	29 days	Anti-spike IgG (63%)	Age, arterial hypertension, and immunosuppression other than CNI monotherapy
Shostak *et al*[58]	*Lancet Respir Med*	BNT162b2	Lung transplant recipient (168)	16 days	Anti-spike IgG (18%)	Treatment with mTOR inhibitor or antimetabolites
Strauss *et al*[59]	*Liver Transpl*	BNT162b2 or mRNA-1273	LTR (161)	30 days	Anti-RBD IgG (81%)	Treatment with antimetabolites, vaccination with BNT162b2 vaccine
Stumpf *et al*[60]	*Lancet Reg Health Eur*	BNT162b2 or mRNA-1273	KTR (368)	4–5 weeks	SARS-CoV-2 IgG/IgA (65%)	Immunosuppressive drug number, vaccination with BNT162b2 vaccine

Anti-RBD IgG: IgG antibody against receptor-binding domain; Anti-spike IgG: IgG antibody against spike protein; ATG: Antithymocyte globulin; CNI: Calcineurin inhibitors; COVID-19: Coronavirus disease 2019; HC: Healthy control; HTR: Heart transplant recipient; Ig: Immunoglobulin; KTR: Kidney transplant recipient; LTR: Liver transplant recipient; MMF: Mycophenolate mofetil; MPA: Mycophenolic acid; mTOR: Mammalian target of rapamycin; NA: Not available; NAb: Neutralizing antibody; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; STOR: Solid organ transplantation recipient.

SOTRs.[57,67] Devresse *et al*[48] showed that KTRs with higher SARS-CoV-2 antibodies were more likely to mount a T-cell response. Interestingly, some SOTRs without an antibody response may exhibit a T-cell response.[48]

The extremely weak immune response to two doses of the SARS-CoV-2 vaccine urges the administration of a third dose of vaccine in SOTRs. Among those who were seronegative after a two-dose course of mRNA vaccination,

the third dose induced a serological response in no more than 50% SOTRs.[68-71] In addition, Caillard *et al*[72] evaluated the fourth dose of mRNA in KTRs who did not respond adequately after three doses and found that 50% of patients reached the threshold of anti-spike IgG titers.

Overall, SOTRs exhibited extremely weak immune responses to the COVID-19 vaccine and should be vaccinated before transplantation whenever possible. In addition, humoral responses should be monitored especially in those who are more likely to show a suboptimal immune response, and additional boosters may be needed to potentiate immune responses in SOTRs.

Patients with anti-CD20 treatment

Multiple studies have indicated that patients receiving anti-CD20 treatment are at higher risk of severe COVID-19.[73,74] Anti-CD20 treatment is used to treat B-cell-mediated malignant tumors and autoimmune diseases but could lead to non-specific and overall suppression of humoral immunity in treated patients. Thus, the immune response to COVID-19 vaccination in patients receiving CD20 monoclonal antibodies was significantly impaired [Table 4]. A recent study compared the seroconversion rate and average antibody titer in 478 patients with autoimmune diseases (including rheumatoid arthritis and systemic lupus erythematosus) and 502 HCs after receiving two doses of the mRNA vaccine.[75] They found that patients with autoimmune diseases who commonly used rituximab or MMF had significantly lower seroconversion rates and average antibody titers than HCs.[75] These data imply that anti-CD20 treatment might lead to a suppressed humoral response. Boekel *et al*[76] performed an observational study to examine the immune response of patients with autoimmune diseases after receiving COVID-19 vaccines and found that significantly reduced anti-RBD antibody response was detected among patients treated with CD20 monoclonal antibodies. Apostolidis *et al*[77] found that, although no significant difference between antigen-specific CD4 and CD8 T cell responses was observed, the antibody response of patients with multiple sclerosis treated with CD20 monoclonal antibody after two doses of mRNA vaccine was significantly lower than that of HCs. Thus, anti-CD20 treatment suppressed the humoral response but not the cellular response to COVID-19 vaccines. In another study, however, Moor *et al*[78] reported that in patients receiving anti-CD20 treatment, 49% detected antibody response and 32% detected T-cell response after 1.79 months of vaccination with two doses of mRNA vaccine. The suppressive degree of anti-CD20 treatment on the humoral response to COVID-19 vaccines might be due to different doses and durations of anti-CD20 treatment in

Table 4: Summary of studies on humoral immune response to COVID-19 vaccination in anti-CD20-treated patients compared with HCs.

Reference	Journal	Vaccine	Study population (*n*)	Detection time points after full course vaccination	Detected parameters (positivity)	Findings
Ferri *et al*[75]	*J Autoimmun*	BNT162b2 or mRNA-1273	Autoimmune diseases (26)	1–3 weeks	IgG-NAb (53.8%)	Rituximab treatment was associated with higher odds of vaccine non-response
Boekel *et al*[76]	*Lancet Rheumatol*	Unlimited	Autoimmune diseases (27)	1–5 months	Anti-RBD IgG (43%)	Lower seroconversion rates and antibody titers in patients with anti-CD20 therapy
Apostolidis *et al*[77]	*Nat Med*	BNT162b2 or mRNA-1273	Multiple sclerosis (20)	25–30 days	Anti-spike (88.89%) Anti-RBD IgG (50%)	Lower anti-spike and RBD antibody levels in patients with anti-CD20 therapy
Moor *et al*[78]	*Lancet Rheumatol*	BNT162b2 or mRNA-1273	B cell-mediated malignancies and autoimmune disorders (96)	1.79 months	Anti-spike IgG (49%)	Lower anti-spike antibody levels in patients with anti-CD20 therapy
van der Togt *et al*[79]	*Rheumatology*	Unlimited	Rheumatoid arthritis (196)	2–6 weeks	Anti-SARS-CoV-2 IgG (28%)	The response rate was significantly lower for patients receiving 1000 mg rituximab compared with those receiving 200 mg rituximab

Anti-RBD IgG: IgG antibody against receptor-binding domain; Anti-spike IgG: IgG antibody against spike protein; COVID-19: Coronavirus disease 2019; HC: Healthy control; Ig: Immunoglobulin; NAb: Neutralizing antibody; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

various conditions. A single-center observational study reported that after adjusting for relevant confounding factors, the seroconversion rate of patients with rheumatoid arthritis treated with 200 mg rituximab after receiving two doses of mRNA or virus vector COVID-19 vaccines was significantly higher than that of patients treated with 1000 mg rituximab.[79]

After COVID-19 vaccination, patients receiving anti-CD20 medication displayed severely impaired humoral responses, but potent T cell responses were preserved. In the absence of a humoral response, whether a vaccine-induced T-cell response exerts protective effects against SARS-CoV-2 infection is still unclear. Thus, the real-world effectiveness of the COVID-19 vaccine in patients receiving anti-CD20 therapy still needs to be confirmed.

Perspective and Challenges

Studies have demonstrated prolonged viral shedding and evolution in SARS-CoV-2-infected immunocompromised populations and suboptimal immune responses to COVID-19 vaccines in immunocompromised populations compared with the general populations.[80,81] However, as shown in immunocompromised populations, the COVID-19 vaccine is still helpful for decreasing the disease severity and hospitalization in these immunocompromised individuals.[82]

In most clinical studies conducted on immunocompromised populations, antibody levels or seroconversion rates are used as surrogate endpoints for vaccine efficacy. However, data are still needed to fully elucidate whether COVID-19 vaccination is protective against SARS-CoV-2 infection, hospitalization, severe diseases, and death in real-world settings. As shown in the general population, a booster dose can partially restore omicron cross-neutralization by neutralizing antibodies.[83] Thus, booster vaccination might be needed for immunocompromised populations, which should be fully evaluated. As neutralizing antibodies wane over time, longitudinal studies are needed to determine the dynamics of vaccine-induced antibodies in immunocompromised populations, which might shed light on when to deliver a booster vaccination.

In addition to humoral immunity, the T-cell immune response is important for protection against viral infections. A recent study conducted in rhesus macaques showed that cellular immunity contributes to protection against viral infection in the context of sub-protective antibody titers.[84] In immunocompromised populations, especially those receiving anti-CD20 treatment, SARS-CoV-2 specific-T cell activity could be detected in some individuals without a detectable humoral response. Although the cellular immunity induced by COVID-19 vaccination retains the ability to recognize SARS-CoV-2, including omicron variant,[85] the real-word protective effects mediated by the cellular immune response in the absence of humoral response are still unclear.

As SARS-CoV-2 is a zoonotic RNA virus with a high mutation rate, the currently dominant omicron variant may result from the evolution in immunocompromised patients.[86] Thus, to prevent further emergence of more dangerous and contagious variants, primary COVID-19 vaccination, especially booster vaccination, is highly recommended. Unfortunately, many advanced HIV-infected patients, especially those in areas within low vaccine-coverage, such as sub-Saharan Africa, cannot get access to COVID-19 vaccines. Accelerating the pace of global vaccination and establishing herd immunity to end the COVID-19 pandemic are urgently needed. Furthermore, with the prevalence of the omicron variant, most authorized vaccines are limited in inducing mucosal immunity.[87] Thus, novel vaccines that broadly target various variants or intranasal vaccines that elicit mucosal immunity should be developed to better protect vulnerable immunocompromised populations.

In all, no additional adverse effects of COVID-19 vaccination were reported, and COVID-19 vaccination is safe in secondary immunocompromised patients.[21,24,27] However, more clinical translational studies are needed to determine the real-world efficacy of various types of COVID-19 vaccines in immunocompromised populations and how best to protect these patients. This will involve determining the most suitable vaccine type, dose, and delivery schedule for immunocompromised patients, and whether a heterologous vaccination schedule is better than homologous vaccination. In addition, as these immunocompromised populations remain at risk of SARS-CoV-2 infection even after vaccination, regular epidemic prevention and control measures including masking and social distancing, should be implemented.

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Conflicts of interest

None.

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