

TO THE EDITOR:

Vaccine-boosted convalescent plasma therapy for patients with immunosuppression and COVID-19

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Although severe coronavirus disease 2019 (COVID-19) and death from COVID-19 are generally preventable in immunocompetent people in areas of the world with sufficient supply of COVID-19 vaccines and therapeutics, patients with immunosuppression have impaired immunogenicity to COVID-19 vaccines and remain at high risk of complications and death.^{1,2} Convalescent plasma represents a passive antibody therapy that has been widely used to treat COVID-19^{3,4} and is recommended for use in patients with immunosuppression or those who lack antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).^{5,6} The beneficial effects associated with passive antibody therapy, including both COVID-19 convalescent plasma and antispikes monoclonal-antibody treatments, are primarily conferred by neutralizing antibodies which target SARS-CoV-2 and promote viral clearance.^{7,8} As SARS-CoV-2 evolves, new variants of concern have emerged which evade available antispikes monoclonal antibodies, particularly among patients with immunosuppression.^{9,10} However, high-titer COVID-19 convalescent plasma continues to be effective against variants of concern because of its broad-spectrum immunomodulatory properties.¹¹

In this context, there is interest in COVID-19 convalescent plasma collected from persons who have been both naturally infected with SARS-CoV-2 and vaccinated against SARS-CoV-2 (herein referred to as “vax-plasma”). Vax-plasma typically has 10 to 100 times higher antibody titers than standard COVID-19 convalescent plasma¹² and may be a promising COVID-19 treatment among patients with immunosuppression.¹³⁻¹⁵ As a proof of concept, we report the clinical course of 31 immunocompromised patients who were hospitalized with COVID-19 and treated with vax-plasma after previously receiving other COVID-19-specific therapies without durable symptom resolution.

This retrospective single-center study was conducted at Mayo Clinic (Rochester, MN) from 1 July 2021 to 1 September 2022. Patient follow-up was continued until death or most recent follow-up and the median follow-up time was 176 days. Immunocompromised patients with active COVID-19 infection, confirmed by SARS-CoV-2-specific reverse transcription polymerase chain reaction, were eligible to receive vax-plasma. The Mayo Clinic Institutional Review Board determined that this study met the criteria for exemption. Informed consent was waived. Only patients of Mayo Clinic with research authorization were included.

Eligible vax-plasma donors included individuals who had a PCR-confirmed diagnosis of COVID-19 and had received at least 1 dose of a SARS-CoV-2 vaccine. All donors experienced mild to moderate symptoms and met the national blood donor selection criteria. Vax-plasma was collected at least 2 weeks and up to 6 months after the complete resolution of COVID-19 symptomatology. Antibody titers of vax-plasma units met the minimum threshold required by the US Food and Drug Administration

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Requestors may be required to sign a data use agreement. Data sharing must be compliant with all applicable Mayo Clinic policies and those of the Mayo Clinic Institutional Review Board.

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for high titer anti-SARS-CoV-2 antibodies, but precise antibody titers were not evaluated. The treatment schedule of vax-plasma transfusions was not standardized. Patients received the number of vax-plasma units deemed appropriate by their clinicians.

A total of 31 consecutive patients treated with vax-plasma were included. Key demographic and clinical characteristics of the study population are provided in Tables 1 and 2. The median age of patients treated with vax-plasma was 63 years (range, 16-84), and 35% (11 of 31 patients) were female. Of these, 21 patients were treated for hematological malignancies, 6 patients were treated for rheumatic diseases, 3 patients had received a SOT, 1 patient was treated for multiple sclerosis, 1 patient was treated for a brain tumor, and 1 patient was diagnosed with CVID during COVID-19 disease. Sixteen patients had received anti-CD20 monoclonal antibodies within the last 6 months and 5 patients had been treated with Bruton tyrosine kinases inhibitors within the last 6 months—both of which have been associated with impaired immunogenicity.^{2,16}

Key descriptions of the clinical course of COVID-19 and vax-plasma transfusion are provided in Tables 1 and 2. Patients had COVID-19 symptoms for a median of 29 days (range, 1-389) before receiving vax-plasma transfusion, and about half (16 of 31 patients) had protracted COVID-19 with symptomology persisting for 4 weeks or more before receiving vax-plasma transfusion. All patients received previous or concomitant therapies for COVID-19-specific treatments, including remdesivir (30 of 31 patients), neutralizing antispikes monoclonal antibodies (7 of 31 patients), or steroids (26 of 31 patients). Because of the persistent nature of their infections, many patients had received combinations and multiple rounds of COVID-19-specific treatments.

At the time of vax-plasma transfusion, 6% (2 of 31 patients) had been previously hospitalized and treated in the outpatient setting, 14 patients were hospitalized and not receiving supplemental oxygen, 12 patients were hospitalized and required oxygen by noninvasive ventilation, and 3 patients were hospitalized and required invasive mechanical ventilation. Patients were transfused with a median of 2 units of vax-plasma (range, 1-11).

No serious adverse effects associated with transfusion of vax-plasma were observed. The overall survival rate after transfusion of vax-plasma was 84% (26 of 31 patients), including 7 of 12 patients (58%) who had been admitted to the intensive care unit. Both patients who received transfusion of vax-plasma in the outpatient setting after COVID-19-related hospitalization survived and demonstrated rapid improvement in symptoms within 5 days of vax-plasma transfusion. Among patients who received vax-plasma transfusion in the inpatient setting, 59% (17 of 29 patients) demonstrated rapid clinical improvement and were discharged within 5 days of vax-plasma transfusion. Among the 7 patients who survived and did not show rapid clinical improvement, the median time to discharge from date of vax-plasma transfusion was 30 days (range, 7-109 days). A total of 5 patients died despite transfusion of vax-plasma. All 5 of these patients were admitted to the intensive care unit at the time of vax-plasma transfusion, including all 3 patients who required invasive mechanical ventilation and 2 patients who required oxygen by noninvasive ventilation.

This case series reports the clinical benefit associated with transfusion of vax-plasma in 31 consecutive immunocompromised patients, many with protracted COVID-19 disease. Although

Table 1. Characteristics of 31 immunocompromised patients with protracted COVID-19 who received vax-plasma transfusion

Characteristics (N = 31)	Data
Age, median (range), y	63 (16-84)
Females/males, n	11/20
Hematological malignancies, n	21*
CLL	5 (24)
MCL	5 (24)
MM	4 (19)
AML	2 (10)
DLBCL	2 (10)
MALT lymphoma	1 (5)
ALL	1 (5)
FL	1 (5)
Other immunosuppressive conditions, n	12*
RA	4 (33)
Systemic lupus erythematosus	2 (17)
SOT†	3 (25)
Multiple sclerosis	1 (8)
CVID	1 (8)
Brain tumor (DL-GNT)	1 (8)
Active immunosuppressive treatment‡, n (%)	
Anti-CD20 therapy	16 (52)
Bruton tyrosine kinase inhibitors	5 (16)
CAR T-cell therapy	3 (10)
COVID-19 severity (WHO score§)	
3	2 (6)
4	14 (45)
5-6	12 (39)
7	3 (10)
Previous COVID-19-specific treatments, n (%)	
Remdesivir	30 (97)
Steroids	26 (84)
mAb	7 (23)
Vaccinated against SARS-CoV-2, n (%)	21 (68)
Hospital admission, n (%)	
Inpatient	29 (94)
ICU	12 (39)
Overall survival, n (%)	26 (84)

Unless otherwise noted, data are presented as number (%).

ALL, Acute lymphoblastic leukemia; AML, acute myeloid leukemia; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; CVID, common variable immune deficiency; DLBCL, diffuse large B-cell lymphoma; DL-GNT, diffuse leptomeningeal disseminated glioneuronal tumor; FL, follicular lymphoma; ICU, intensive care unit; MALT, mucosa-associated lymphoid tissue; mAb, neutralizing antispikes monoclonal antibodies; MCL, mantle cell lymphoma; MM, multiple myeloma; RA, rheumatoid arthritis; SOT, solid organ transplant; WHO, World Health Organization.

*Note that hematological malignancies and other immunosuppressive conditions are not mutually exclusive. Two patients had multiple malignant diagnoses— CVID and MALT lymphoma (1 patient) and lupus and multiple kidney transplants (1 patient).

†SOTs included heart (1 patient), both liver and kidney transplant (1 patient), and kidney transplant (1 patient).

‡Active immunosuppressive treatment included immunosuppressive treatment received any time during the 6 months before vax-plasma transfusion.

§WHO Disease Severity Scale: 3, not hospitalized; 4, hospitalized, no supplemental oxygen; 5, hospitalized, nonhigh flow supplemental oxygen; 6, hospitalized, high flow supplemental oxygen; 7, hospitalized, intubated or extracorporeal membrane oxygenation; 8, deceased.

Table 2. Characteristics of 31 immunocompromised patients with protracted COVID-19 who received vax-plasma transfusion stratified by patient

No.	Diagnosis	Before vax-plasma				Vax-plasma				Outcomes		
		Prev. hosp.	Previous therapies			WHO*	ICU	Time to Tx, d	Transfusions, No.	Discharge, d	Survival	
			R	S	mAb							CCP19
1	CLL	1	●	●			6	Yes	2	2	3	Yes
2	CLL	1	●	●		●	4	–	386	1	1	Yes
3	CLL	0	●		●		4	–	31	2	5	Yes
4	CLL	0	●				4	–	41	2	1	Yes
5	CLL	0	●	●	●		7	Yes	29	2	–	No
6	MCL	11	●	●		●	3	–	281	6	–	Yes
7	MCL	1	●	●		●	4	–	389	2	3	Yes
8	MCL	0	●				4	–	1	2	1	Yes
9	MCL	0	●	●			5	Yes	14	1	3	Yes
10	MCL	0	●	●			5	–	1	1	3	Yes
11	MM	1	●	●	●		5	Yes	13	3	16	Yes
12	MM	0	●	●			4	–	3	1	4	Yes
13	MM	0	●	●	●		4	–	25	1	20	Yes
14	MM	0	●	●			4	–	55	1	4	Yes
15	AML	2	●	●			5	–	32	2	13	Yes
16	AML	0	●	●			7	Yes	2	1	–	No
17	DLBCL	2	●	●	●		5	–	41	2	4	Yes
18	DLBCL	1		●			6	Yes	32	2	–	No
19	ALL	0	●				4	–	1	1	19	Yes
20	FL	1	●	●	●		4	–	161	2	1	Yes
21	RA	2	●	●			3	–	340	2	–	Yes
22	RA	1	●	●	●		5	–	31	3	4	Yes
23	RA	0	●	●			4	–	3	2	1	Yes
24	RA	1	●	●			5	Yes	65	1	–	No
25	Lupus	1	●	●			4	Yes	35	1	109	Yes
26	SOT	2	●	●			6	Yes	6	1	23	Yes
27	SOT	0	●	●			5	Yes	3	2	7	Yes
28	SOT, Lupus	0	●	●			7	Yes	19	2	–	No
29	MS	0	●	●			4	–	23	1	4	Yes
30	CVID, MALT	2	●	●		●	5	Yes	384	11	5	Yes
31	DL-GNT	0	●				4	–	2	1	3	Yes

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CCP19, coronavirus disease 2019 convalescent plasma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; DL-GNT, diffuse leptomeningeal disseminated glioneuronal tumor; FL, follicular lymphoma; mAb, neutralizing anti-spike monoclonal antibody; ICU, intensive care unit admission; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; MM, multiple myeloma; No., number; Prev. hosp., number of previous hospitalizations for COVID-19; R, remdesivir; RA, rheumatoid arthritis; S, steroid; Tx, treatment; WHO, World Health Organization.

● Indicate previous or concomitant therapies for COVID-19 specific treatments received by each patient.

*WHO Disease Severity Scale: 3, not hospitalized; 4, hospitalized, no supplemental oxygen; 5, hospitalized, nonhigh flow supplemental oxygen; 6, hospitalized, high flow supplemental oxygen; 7, hospitalized, intubated or extracorporeal membrane oxygenation; 8, deceased.

COVID-19–specific treatments induced a transient improvement in symptomatology for all patients, all COVID-19–specific treatments failed to sustainably improve the clinical course of COVID-19. However, vax-plasma was associated with rapid improvement of clinical symptoms and hospital discharge in 17 of 29 patients treated in the inpatient setting. Although it is possible that patients were recovering before transfusion of vax-plasma, the close temporal association between transfusion, and rapid clinical improvement and hospital discharge, suggest that vax-plasma was likely

associated with a meaningful clinical benefit in this patient population.^{17,18}

Importantly, we did not find a clinical benefit associated with transfusion of vax-plasma among the 3 patients who required invasive mechanical ventilation. In line with previous findings^{14,19-21} and the biological principles of antibody therapy,²² the benefit of vax-plasma was most apparent in patients who were treated before disease progression to invasive mechanical ventilation.

Several limitations resulted from the design of this study and the contextual challenges of clinical research during a pandemic,²³ which may highlight areas for future investigation. First, SARS-CoV-2 serology was not performed. However, it is highly likely that these patients were unable to generate an endogenous antibody response to COVID-19 infection. Second, the interpretation of these results is limited by the open-label design, the lack of a randomized placebo (control) group, and the small sample size. However, it should be noted that vax-plasma was a therapy of last resort in these patients, and the patients had multiple comorbidities beyond their immune suppression.

Despite the enumerated limitations of this study, our data suggest that transfusion of vax-plasma is safe and effectively transfers COVID-19–neutralizing antibodies to patients with immunosuppression and protracted COVID-19. From the amalgam of evidence,^{4,5} it is clear that the benefit of vax-plasma (or standard convalescent plasma or antispikes monoclonal antibody therapy) is least apparent in patients who receive antibody therapy later in the disease course after the need for invasive mechanical ventilation. The extent to which vax-plasma might be a preferred first-line therapy in patients with immunosuppression or reserved for use in patients that have failed other therapies warrants further discussion and systematic study.

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