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

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

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Although severe coronavirus disease 19 (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 immunosuppressed patients or those who lack antibodies against SARS-CoV-2[5,6]. The beneficial effects associated with passive antibody therapy, including both COVID-19 convalescent plasma and anti-spike 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 (VOCs) have emerged which evade available anti-spike monoclonal antibodies, particularly among immunosuppressed patients[9,10]. However, high-titer COVID-19 convalescent plasma continues to be effective against VOCs 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 plasma[12] and may be a promising COVID-19 treatment among immunosuppressed patients[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 therapeutics without durable symptom resolution.

This retrospective single-center study was conducted at Mayo Clinic (Rochester, Minnesota) 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 Mayo Clinic patients 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 one 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 US FDA 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.

Thirty-one 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 to 84 years), and 35% (11 of 31 patients) were female. Twenty-one patients were treated for hematologic malignancies, six patients were treated for rheumatic diseases, three patients had received a solid organ transplant, one patient was treated for multiple sclerosis, one patient was treated for a brain tumor, and one patient was diagnosed with common variable immune deficiency during COVID-19 disease. Sixteen patients had received anti-CD20 monoclonal antibodies within the last six months and five patients had been treated with Bruton tyrosine kinases inhibitors within the last six 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 to 389 days) before receiving vax-plasma transfusion, and about half (16 of 31 patients) had protracted COVID-19 with symptomology persisting for four 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 anti-spike monoclonal antibodies (7 of 31 patients), or steroids (26 of 31 patients). Due to 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 to 11 units).

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 to 109 days). Five patients died despite transfusion of vax-plasma. All five of these patients were admitted to the intensive care unit at the time of vax-plasma

transfusion, including all three patients who required invasive mechanical ventilation and two 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 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 co-morbidities 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 anti-spike 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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Authorship

Study conception and design: J.G.R., E.K.G., M.J.J., and J.W.S. Acquisition, analysis, or interpretation of data: J.G.R., E.K.G., J.E.J., E.S.T., and J.R.S. Drafting of the manuscript: J.G.R., E.K.G., M.J.J., and J.W.S. Administrative, technical, or material support: J.E.J., R.R.R., R.G., R.T.H., E.S.T., J.R.S., J.L.W., S.A.P., and N.E.K. All authors contributed to revising the manuscript, and all authors approved the final version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Data Availability

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References

1. Fendler A, de Vries EGE, GeurtsvanKessel CH, et al. COVID-19 vaccines in patients with cancer: immunogenicity, efficacy and safety. *Nat Rev Clin Oncol*. 2022;19(6):385-401.
2. Ribas A, Dhodapkar MV, Campbell KM, et al. How to Provide the Needed Protection from COVID-19 to Patients with Hematologic Malignancies. *Blood Cancer Discov*. 2021;2(6):562-567.
3. Senefeld JW, Johnson PW, Kunze KL, et al. Access to and safety of COVID-19 convalescent plasma in the United States Expanded Access Program: A national registry study. *PLoS Med*. 2021;18(12):e1003872.
4. Klassen SA, Senefeld JW, Johnson PW, et al. The Effect of Convalescent Plasma Therapy on Mortality Among Patients With COVID-19: Systematic Review and Meta-analysis. *Mayo Clin Proc*. 2021;96(5):1262-1275.
5. Estcourt LJ, Cohn CS, Pagano MB, et al. Clinical Practice Guidelines From the Association for the Advancement of Blood and Biotherapies (AABB): COVID-19 Convalescent Plasma. *Ann Intern Med*. 2022;0(0):null.
6. Senefeld JW, Klassen SA, Ford SK, et al. Use of convalescent plasma in COVID-19 patients with immunosuppression. *Transfusion*. 2021;61(8):2503-2511.
7. Bloch EM, Crowe EP, Tobian AAR. Coronavirus Disease 2019 Convalescent Plasma and the Severe Acute Respiratory Syndrome Coronavirus 2 Neutralizing Titer. *J Infect Dis*. 2021;223(5):740-742.
8. Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19. *N Engl J Med*. 2021;385(23):e81.
9. Pommeret F, Colomba J, Bigenwald C, et al. Bamlanivimab + etesevimab therapy induces SARS-CoV-2 immune escape mutations and secondary clinical deterioration in COVID-19 patients with B-cell malignancies. *Ann Oncol*. 2021;32(11):1445-1447.

10. Jary A, Marot S, Faycal A, et al. Spike Gene Evolution and Immune Escape Mutations in Patients with Mild or Moderate Forms of COVID-19 and Treated with Monoclonal Antibodies Therapies. *Viruses*. 2022;14(2).
11. Li M, Beck EJ, Laeyendecker O, et al. Convalescent plasma with a high level of virus-specific antibody effectively neutralizes SARS-CoV-2 variants of concern. *Blood Adv*. 2022;6(12):3678-3683.
12. Schmidt F, Weisblum Y, Rutkowska M, et al. High genetic barrier to SARS-CoV-2 polyclonal neutralizing antibody escape. *Nature*. 2021;600(7889):512-516.
13. Ordaya EE, Abu Saleh OM, Stubbs JR, Joyner MJ. Vax-Plasma in Patients With Refractory COVID-19. *Mayo Clin Proc*. 2022;97(1):186-189.
14. Hueso T, Pouderoux C, Pere H, et al. Convalescent plasma therapy for B-cell-depleted patients with protracted COVID-19. *Blood*. 2020;136(20):2290-2295.
15. Thompson MA, Henderson JP, Shah PK, et al. Association of Convalescent Plasma Therapy With Survival in Patients With Hematologic Cancers and COVID-19. *JAMA Oncol*. 2021.
16. Greenberger LM, Saltzman LA, Senefeld JW, Johnson PW, DeGennaro LJ, Nichols GL. Antibody response to SARS-CoV-2 vaccines in patients with hematologic malignancies. *Cancer Cell*. 2021;39(8):1031-1033.
17. Clark E, Guilpain P, Filip IL, et al. Convalescent plasma for persisting COVID-19 following therapeutic lymphocyte depletion: a report of rapid recovery. *Br J Haematol*. 2020;190(3):e154-e156.
18. Gachoud D, Pillonel T, Tsilimidos G, et al. Antibody response and intra-host viral evolution after plasma therapy in COVID-19 patients pre-exposed or not to B-cell-depleting agents. *Br J Haematol*. 2022.
19. Joyner MJ, Carter RE, Senefeld JW, et al. Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19. *N Engl J Med*. 2021;384(11):1015-1027.
20. Gonzalez SE, Regairaz L, Salazar MR, et al. Timing of convalescent plasma administration and 28-day mortality in COVID-19 pneumonia. *J Investig Med*. 2022;70(5):1258-1264.
21. Park H, Tarpey T, Liu M, et al. Development and Validation of a Treatment Benefit Index to Identify Hospitalized Patients With COVID-19 Who May Benefit From Convalescent Plasma. *JAMA Netw Open*. 2022;5(1):e2147375.
22. Casadevall A, Pirofski LA, Joyner MJ. The Principles of Antibody Therapy for Infectious Diseases with Relevance for COVID-19. *mBio*. 2021;12(2).
23. Rojek AM, Horby PW. Modernising epidemic science: enabling patient-centred research during epidemics. *BMC Med*. 2016;14(1):212.

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

Characteristics (N = 31)	Data
Age, median (range), years	63 (16-84)
Females/males, n	11 / 20
Hematological malignancies, n	21[†]
Chronic lymphocytic leukemia	5 (24)
Mantle cell lymphoma	5 (24)
Multiple myeloma	4 (19)
Acute myeloid leukemia	2 (10)
Diffuse large B-cell lymphoma	2 (10)
MALT lymphoma	1 (5)
Acute lymphoblastic leukemia	1 (5)
Follicular lymphoma	1 (5)
Other immunosuppressive conditions, n	12†
Rheumatoid arthritis	4 (33)
Systemic lupus erythematosus	2 (17)
Solid organ transplant*	3 (25)
Multiple sclerosis	1 (8)
Common variable immune deficiency	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 to 6	12 (39)
7	3 (10)
Previous COVID-19-specific treatments, n (%)	
Remdesivir	30 (97)
Steroids	26 (84)
Neutralizing anti-spike monoclonal antibodies	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 n (%).

Abbreviations: CAR, chimeric antigen receptor; COVID-19, coronavirus disease 2019; DL-GNT, diffuse leptomeningeal disseminated glioneuronal tumor; ICU, intensive care unit; MALT, mucosa-associated lymphoid tissue; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

*Solid organ transplants included heart (1 patient), both liver and kidney transplant (1 patient), and kidney transplant (1 patient)

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

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

Active immunosuppressive treatment

§WHO Disease Severity Scale: 3, not hospitalized; 4, hospitalized, no supplemental oxygen; 5, hospitalized, non-high 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.

		Before vax-plasma					Vax-Plasma				Outcomes	
			Previous Therapies								Discharge, days	Survival
No.	Diagnosis	Prev. Hosp.	R	S	mAb	CCP19	WHO	ICU	Time to Tx, days	Transfusions, No.		
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

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CCP19; coronavirus disease 2019 convalescent plasma; CLL, chronic lymphocytic leukemia; CVID, common variable immune deficiency; DL-GNT, diffuse leptomeningeal disseminated glioneuronal tumor; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; mAb, neutralizing anti-spike monoclonal antibody; ICU, intensive care unit admission; 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; SOT, solid organ transplant; Tx, treatment.

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