Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

and may limit the appropriate application of interventions.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://ww.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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Vax-Plasma in Patients With Refractory COVID-19

To the Editor: Convalescent plasma (CP) therapy uses neutralizing antibodies harvested from recovered patients to treat viral infections, including severe acute respiratory syndrome coronavirus (SARS-CoV) and influenza A.[1] The emerging data from randomized controlled trials and observational studies suggest—consistent with historical precedent—that CP therapy has limited efficacy in severely ill patients with coronavirus disease 2019 (COVID-19) treated late in the disease course. However, early treatment with high-titer CP exhibits signs of efficacy.[2] Additionally, CP use in immunocompromised hosts unable to generate endogenous antibodies suggests a mortality benefit and rapid clinical improvement.[3,4] One group of patients who benefit from CP therapy are those with primary or secondary B-cell deficiencies with a high risk of severe COVID-19 due to their reduced ability to produce neutralizing antibodies.[5,6] These patients can also have prolonged refractory COVID-19 that can last many months and include the generation of novel viral variants. In this context, Vax-plasma is CP from patients who have recovered from natural infection and have been subsequently vaccinated. It can have 10 to 100 times higher antibody titers than does standard high-titer CP with a broad coverage of known COVID-19 variants.[7] Herein, we present our first experience using Vax-plasma in an immunocompromised patient with refractory COVID-19.

In the fall of 2020, a 68-year-old patient with a history of mantle cell lymphoma and recently diagnosed with COVID-19 presented in the emergency department with shortness of breath, cough, and fever. His medical history was remarkable for metastatic mantle cell lymphoma treated with 6 cycles of rituximab and bendamustine, followed by an autologous stem cell transplant 2 years before this admission. He received maintenance therapy with rituximab every 2 months with the last infusion 2 months before this presentation. His examination was remarkable for nonlabored breathing and coarse crackles in both bases. His white blood cell count was 3800 cells/μL; lymphocyte count, 140 cells/μL; C-reactive protein level, 141 mg/L; ferritin level, 849 μg/L; and D-dimer level, 19,418 ng/mL. Chest radiography revealed airspace opacities bilaterally, and computed tomography of the lungs revealed numerous ground-glass opacities consistent with COVID-19 pneumonia (Figure 1 A and B). The patient received remdesivir for 5 days but developed hypoxia, with repeated lung imaging revealing worsening patchy infiltrates. The patient next received broad-spectrum antibiotics along with dexamethasone and

remdesivir for 5 additional days. His infectious disease work-up was negative for superimposed infection, so the broad-spectrum antibiotics were discontinued. In addition, 2 U of high-titer CP was administered on consecutive days. His fever and hypoxia resolved, his C-reactive protein level diminished to 37 mg/L, and the patient was dismissed after being hospitalized for 2 weeks.

Unfortunately, the patient had recurrent episodes of fever, shortness of breath, and hypoxia, requiring intermittent admissions to the intensive care unit and receiving multiple courses of remdesivir, dexamethasone, and high-titer CP, requiring 9 rehospitalizations. He was also diagnosed with pulmonary embolism and cryptogenic organizing pneumonia, receiving anticoagulation and high doses of corticosteroids with initial improvement, but was then rehospitalized with the same symptomatology. He had a persistently positive SARS-CoV-2 polymerase chain reaction result and was diagnosed with refractory COVID-19 (Figure 2).

During his last hospitalization in the summer of 2021, the patient presented again with fever, hypoxia, and persistent pulmonary infiltrates (Figure 1 C and D). He received remdesivir, corticosteroids, and 2 U of high-titer CP. The semiquantitative detection of total antibodies against the SARS-CoV-2 spike protein (Roche Elecsys Anti-SARS-CoV-2 S assay, Roche Diagnostics) resulted 2.9 U/mL after the first infusion of CPT and 4.1 U/mL after the second unit. The IMMUNO-COV SARS-CoV-2 neutralizing antibody test result was negative. As he continued to have hypoxia, Vax-plasma was administered. After the first infusion, the semiquantitative detection of total antibodies against SARS-CoV-2 spike antibody was repeated and resulted greater than 250 U/mL (Roche Elecsys Anti-SARS-CoV-2 S assay). After the second dose of Vax-plasma the following day, the semiquantitative detection of total antibodies resulted greater than 250 U/mL and IMMUNO-COV SARS-CoV-2 neutralizing antibody test resulted positive (level was 286). No adverse

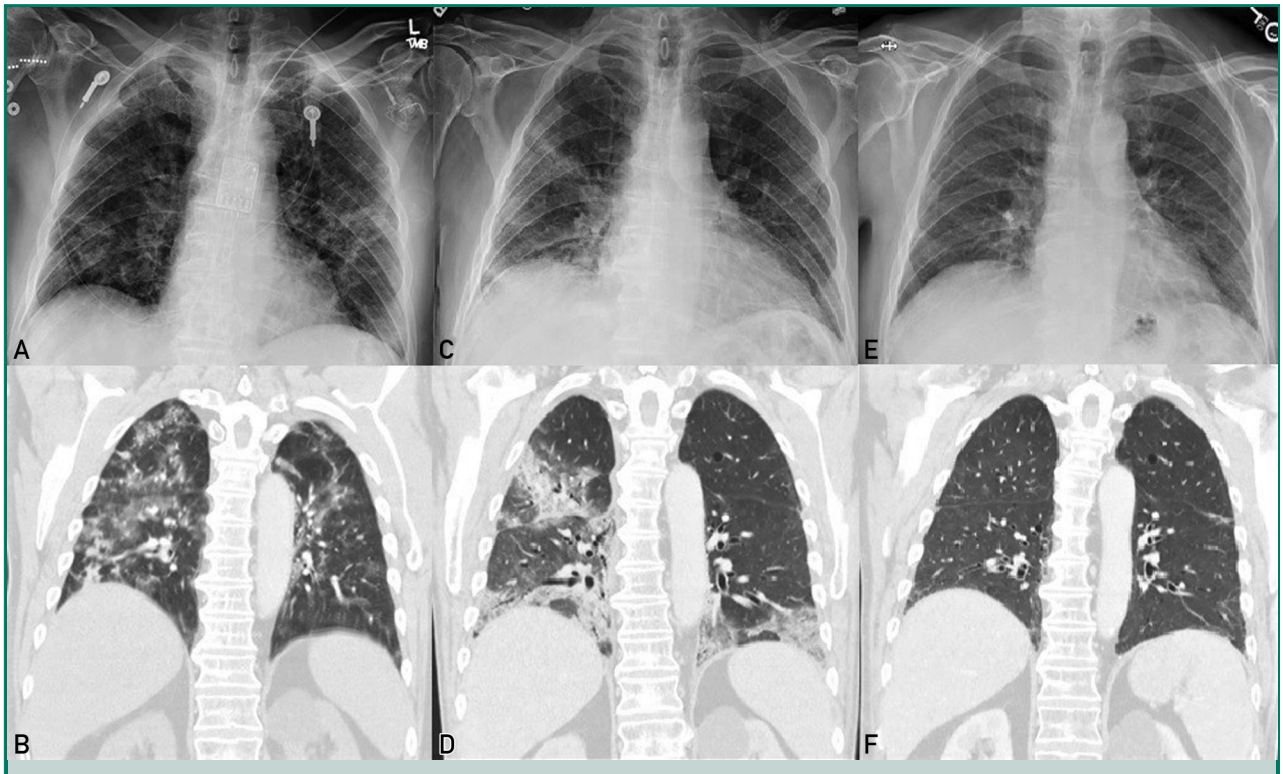

FIGURE 1. Imaging during the patient's illness. Panels A and B correspond to his first hospitalization. Panels C and D correspond to his last hospitalization. Panel E and F correspond to his follow-up visit after receiving Vax-plasma. A, Chest radiography revealing diffuse airspace opacities in both lungs. B, Computed tomography of the chest revealing multiple bilateral consolidations and ground-glass opacities. C, Chest radiography revealing patchy opacities in both lungs with consolidative changes. D, Computed tomography of the chest revealing airspace disease with consolidations. E, Chest radiography revealing near complete interval resolution of patchy bilateral infiltrates. F, Computed tomography of the chest revealing interval resolution of airspace opacities in both lungs.

FIGURE 2. Clinical Course of the Patient With Refractory COVID-19[a,b]

Fever		(+)	(+)	(+)	(+)	(+)	(−)	(+)	(+)	(−)	(+)	(−)
Hypoxia		(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(−)
Lymphocyte absolute count ($\times 10^9$/L)		0.14	0.19	0.28	0.12	0.31	0.09	0.22	0.27	0.16	0.15	ND
C-reactive protein level (mg/L)		141	87	118	ND	162	82	124	106	70	84	<3
Ferritin level (μg/L)		849	1154	ND	7670	4242	4345	3100	1070	791	791	ND
Remdesivir		10 d	(−)	5 d	5 d	(−)	5 d	5 d	5 d	(−)	5 d	(−)
Corticosteroids[c]		5 d	10 d	10 d	10 d	PDN Taper	+ + +	10 d	PDN taper +	PDN taper +	PDN taper +	+
CP		2 U	(−)	2U	(−)	(−)	2 U	2 U	(−)	(−)	2 U	(−)
Vax-plasma		(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	2 U	1 U
	Day 0	Day 8-21 hospitalization	Day 28-38 hospitalization	Day 40-48 hospitalization	Day 78-90 hospitalization	Day 97-109 hospitalization[d]	Day 195-200 hospitalization	Day 226-235 hospitalization[e]	Day 247-254 hospitalization	Day 262-264 hospitalization	Day 269-276 hospitalization	Day 305 follow-up
SARS-CoV-2 PCR	(+)	ND	ND	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(−)
SARS-CoV-2 nudeocapsid antibody		ND	ND	ND	ND	(−)	(−/+)[f]	(−/+)[f]	(+)	(+)	(−)	ND
SARS-CoV-2 spike antibody (U/mL)		ND	ND	ND	ND	ND	ND	1.9	ND	ND	2.9—4.1[g]/>250>250[h]	>250
SARS-CoV-2 neutralizing antibody		ND	ND	ND	ND	ND	ND	ND	ND	ND	(−)[i]/286[j]	ND

[a]COP, cryptogenic organizing pneumonia; COVID-19, coronavirus disease 2019; CP, convalescent plasma; ND, no data; PCR, polymerase chain reaction; PDN, prednisone; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; U, units.

[b]SARS-CoV-2 PCR, Cobas SARS-CoV-2 assay (Roche Molecular Systems, Inc.); SARS-CoV-2 nucleocapsid antibody, Roche Elecsys Anti-SARS-CoV-2 Reagent assay (Roche Diagnostics); SARS-CoV-2 spike antibody, SARS-CoV-2 spike glycoprotein antibody (Roche Elecsys Anti-SARS-CoV-2 S Reagent assay from Roche Diagnostics); SARS-CoV-2 neutralizing antibody, IMMUNO-COV.

[c]Patients received dexamethasone initially between 5 and 10 d and then PDN at different doses after the diagnosis of COP.

[d]Admission was complicated by aspiration pneumonia and COP. PDN 20 mg per day was initiated and then tapered down slowly.

[e]The patient required mechanical ventilation, and nasopharynx and bronchoalveolar lavage samples resulted positive for SARS-CoV-2.

[f]SARS-CoV-2 nucleocapsid antibody test results were negative before receiving CP and then turned positive after receiving two units of high-titer CP.

[g]SARS-CoV-2 spike protein antibody test results after receiving the first and second unit of high-titer CP.

[h]SARS-CoV-2 spike protein antibody test results after receiving the first and second unit of super high-titer CP (Vax-plasma).

[i]SARS-CoV-2 neutralizing antibodies after receiving two units of high-titer CP.

[j]SARS-CoV-2 neutralizing antibodies after receiving two units of super high-titer CP (Vax-plasma).

effects were reported. The patient improved progressively, and on dismissal 7 days later, he was afebrile and not hypoxic. At follow-up, he remained afebrile, with normal oximetry results, and imaging revealed almost complete resolution of pulmonary infiltrates (Figure 1 E and F). He also had a negative SARS-CoV-2 RNA test result 1 month after his last hospitalization and 305 days after his first positive test result. He has subsequently received monthly outpatient infusions of Vax-plasma, and after 10 weeks of follow-up, the patient has not been admitted to the hospital.

To our knowledge, this is the first report of Vax-plasma treatment in a patient with COVID-19 unable to mount normal antibody responses to the disease. Notably, the serum neutralizing antibody response from individuals who have been infected is enhanced after receiving a messenger RNA vaccine and could effectively neutralize an array of COVID-19 variants.[7,8] In conclusion, the use of Vax-plasma is a promising therapy that can be included in the treatment and prevention of COVID-19 in immunocompromised patients.

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Giant Cell Arteritis: The Place of ^{18}F-FDG PET/CT and Serum Haptoglobin Level

To the Editor: I read with great interest the article by Garvey et al.[1] They mentioned that treatment with tocilizumab induced a direct inhibition of the acute phase response, and thus C-reactive protein levels are difficult to interpret. This is why identifying active disease or relapse is a challenge in these patients. ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) has been proposed as a useful tool to assess response and relapse. However, several studies reported that a complete normalization of PET/CT activity occurred in less than 30% of patients while they are in clinical remission.[2,3] The place of ^{18}F-FDG PET/CT in follow-up should be further investigated. Recently, Unizony et al[4] studied several biomarkers in the sample from patients of the Giant Cell Arteritis Actemra trial.[5] They included 30 patients with active disease (16 taking prednisolone and 14 taking tocilizumab). Serum amyloid A1 and A2 and complement factor H were higher in patients with active disease and receiving prednisolone therapy. Interestingly, the haptoglobin blood test, which is an easy and widely available biological test, seems to be higher in patients with active disease and taking tocilizumab. This may be helpful as tocilizumab use will be substantially increased in the next few years. More studies are needed to evaluate the place of ^{18}F-FDG PET/CT and serum haptoglobin level in follow-up and in the diagnosis of relapse.

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