

# Steroid-Resistant Acute Cellular Rejection of the Liver After Severe Acute Respiratory Syndrome Coronavirus 2 mRNA Vaccination

## TO THE EDITOR:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has induced a tremendous toll on our health care system and society, but the rapid development of effective vaccines using novel mRNA technology in less than 1 year represents an unprecedented scientific achievement. In December 2020, the Pfizer-BioNTech (New York, NY, USA and Mainz, Germany) (BNT162b2) and Moderna (Cambridge, MA, USA) (mRNA-1273) vaccines were approved by the US Food and Drug Administration under an Emergency Use Authorization based on phase 2/3 clinical trial data showing high efficacy in preventing symptomatic SARS-CoV-2 infection with a favorable safety profile in more than 70,000 individuals, but recipients of immunosuppressive medications, including liver transplantation (LT) recipients, were excluded from the trials.<sup>(1,2)</sup> In this setting of rapid deployment, little is known of the efficacy and potential risks of novel SARS-CoV-2 vaccination in

LT recipients. We report an episode of steroid-resistant acute cellular rejection (ACR) in an LT recipient occurring after the first dose of the Moderna vaccine.

## Case Report

A 64-year-old woman received a deceased donor LT on August 18, 2020, for cirrhosis attributed to hepatitis C virus and hepatocellular carcinoma. Her hepatitis C virus infection had been cured with direct-acting antiviral medications 4 years earlier. Classes 1 and 2 anti-human leukocyte antigen donor-specific antibodies (DSA) were negative on the day prior to LT. Explant pathology revealed cirrhosis with a single 0.1-cm focus of hepatocellular carcinoma in an otherwise necrotic 2.2-cm nodule, without vascular invasion or lymph node metastasis. She had an unremarkable post-LT course with no episodes of ACR or other LT complications, respiratory infections, fevers, or other symptomatic episodes suggesting symptomatic SARS-CoV-2 infection or exposures to individuals with known SARS-CoV-2 infection. Maintenance immunosuppression consisted of tacrolimus 2 mg twice daily, azathioprine 150 mg daily, and prednisone 5 mg daily, with no missed medication doses, and tacrolimus trough levels were consistently within the goal range (Table 1).

At 5½ months after LT, she received the first dose of the Moderna vaccine. She experienced local soreness and reduced range of motion at the injection site, similar to with previous vaccinations, and reduced sense of smell and mild myalgias for 5 days, after which her symptoms fully resolved and she resumed her usual state of good health. Routine liver test monitoring 6 days prior to the vaccination was normal, and she was advised to begin tapering off prednisone; she decreased it to 2.5 mg daily for 2 weeks starting 1 day after vaccination and then discontinued it entirely.

*Abbreviations: ACR, acute cellular rejection; ATG, antithymocyte globulin; DSA, donor-specific antibodies; IV, intravenous; LT, liver transplantation; RAI, rejection activity index; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.*

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**TABLE 1. Laboratory Testing and Medication Use Before and After SARS-CoV-2 mRNA Vaccination**

Laboratory Testing or Medications	Days Before (-) or After (+) SARS-CoV-2 mRNA Vaccination								
	-90	-30	-6	0	+15	+21	+25	+29	+36
				↑ Vaccine, Prednisone Taper	↑ Biopsy	↑ IV Steroids	↑ Biopsy	↑ ATG	↑ Biopsy
<b>Laboratory testing</b>									
Aspartate aminotransferase, U/L	36	33	39		229	191	188	125	94
Alanine aminotransferase, U/L	26	23	35		199	195	245	229	145
Alkaline phosphatase, U/L	127	162	172		576	522	449	467	437
Bilirubin, mg/dL	0.4	0.7	0.6		6.0	4.9	5.5	5.2	2.7
Albumin, g/dL	4.0	4.2	3.9		3.3	2.0	2.6	2.6	2.3
Tacrolimus, 12-hour trough, ng/mL	8.3	5.8	5.9		8.3	7.0	8.3	11.3	8.6
Cytomegalovirus DNA				Negative					
Hepatitis C virus RNA				Negative					
Herpes simplex virus 1/2 DNA				Negative					
Adenovirus DNA				Negative					
SARS-CoV-2 RNA				Negative					Negative
DSA				Negative			Negative		
SARS-CoV-2 spike protein antibodies									
S1 subunit				Positive			Positive		
Receptor binding domain				Negative			Negative		
<b>Medications</b>									
Tacrolimus, mg/day	4	4	4		4	4	7	4	6
Azathioprine, mg/day	150	150	150		150	150	0	0	0
Mycophenolate mofetil, mg/day	0	0	0		0	0	2000	2000	2000
Prednisone, mg/day	5	5	2.5		20	40	0	0	40
Methylprednisolone, mg/day	0	0	0		0	500	0	95	0
ATG, mg/kg/day	0	0	0		0	0	0	1.0	0

At 11 days after the vaccination, she developed darkened urine, fatigue, and malaise and was found to have newly elevated liver tests. Multiphase liver magnetic resonance imaging, magnetic resonance cholangiopancreatography, Doppler liver ultrasound, and echocardiogram revealed no evidence of biliary obstruction, vascular abnormality, or cardiac dysfunction, and DSA were negative. A transabdominal liver biopsy was obtained and showed mixed portal inflammation, bile duct injury, and endotheliitis consistent with ACR (rejection activity index [RAI] score 4) with central venular dilation and sinusoidal congestion indicating possible hepatic venous outflow obstruction or sinusoidal obstruction syndrome. She was treated with a 3-day course of intravenous methylprednisolone, with azathioprine changed to mycophenolate mofetil because of the concern for possible sinusoidal obstruction syndrome.

The liver test elevation did not improve after intravenous steroid therapy, and a repeat liver biopsy

showed similar histology to the initial biopsy with persistent ACR (RAI score 5) and slightly reduced central venular dilation and sinusoidal congestion. DSA were again negative. She was treated with antithymocyte globulin 1 mg/kg daily for a 6-day duration, and the liver tests gradually decreased. A third liver biopsy after completion of antithymocyte globulin showed improved ACR (RAI score 2) and no central venular dilation or sinusoidal congestion. At 2 and 4 weeks after vaccination, enzyme immunoassay testing was positive for antibodies to the SARS-CoV-2 spike protein S1 subunit, but not the receptor binding domain.

## Discussion

Inactivated or recombinant (nonlive) vaccinations are generally considered to be safe after solid organ

transplantation, with studies showing no increase in allograft rejection after influenza or adjuvanted recombinant zoster vaccination.<sup>(3,4)</sup> Although the Moderna and Pfizer-BioNTech vaccines are the first commercially available lipid nanoparticle-encapsulated mRNA vaccines, the technology has been previously studied in cancer and other infectious diseases, and expert opinion does not implicate the mechanism of action as a likely trigger for allograft rejection.<sup>(5)</sup> Accordingly, both the American Association for the Study of Liver Diseases and the American Society of Transplantation endorse both SARS-CoV-2 mRNA vaccines in LT recipients, although recognizing that safety data are limited.<sup>(5,6)</sup> An online registry, Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-Liver), aims to assess SARS-CoV-2 outcomes in US LT recipients but does not include adverse outcomes related to SARS-CoV-2 vaccination in patients without SARS-CoV-2 infection. A recent European study found a 20% mortality in LT recipients with SARS-CoV-2 infection, markedly higher than in the general population, highlighting the potential benefits of vaccination to protect against severe SARS-CoV-2 infection in LT recipients.<sup>(7)</sup> Furthermore, SARS-CoV-2 infection itself was associated with ACR in 3 of 243 patients. Hypothetical risks of vaccination, such as immune stimulation precipitating graft rejection, as possibly occurred in this case, must therefore be weighed against the known grave consequences of SARS-CoV-2 infection in LT recipients.

We must strongly emphasize that a causal relationship between SARS-CoV-2 mRNA vaccination and the development of ACR cannot be established in this case, with the simultaneous withdrawal of low-dose prednisone representing a major confounder. However, the timing of ACR onset after vaccination and the absence of clinical risk factors typically associated with ACR (young age, preformed or de novo DSA, prior ACR, inadequate immunosuppression adherence or drug levels, autoimmune liver disease etiology) raise the suspicion for a potentially causal association. Outcomes of solid organ transplantation recipients after SARS-CoV-2 mRNA vaccination are currently limited to a single case series of 187 participants (50% Moderna, 50% Pfizer-BioNTech) who had no episodes of ACR; however, the median time since transplantation was 6 years (lower limit interquartile range, 3 years), which may not be generalizable to ACR risk for vaccine recipients in the early period after LT in which ACR is more common.<sup>(8)</sup> Although antispike antibodies to the

S1 subunit and receptor binding domain were used to evaluate immunogenicity in the mRNA vaccine clinical trials and are uncommon in solid organ transplant recipients (detected in only 17% at a median 20 days after the first vaccine dose),<sup>(9)</sup> it is uncertain whether a specific vaccine-elicited antibody response correlates with the more global immune stimulation that might be expected in the setting of allograft rejection.

We present the first reported case of ACR occurring after the first dose of SARS-CoV-2 mRNA vaccination in an LT recipient who simultaneously underwent steroid withdrawal. Based on this single case report, a causal relationship between vaccination and liver allograft rejection remains uncertain, as are the clinical roles of SARS-CoV-2 antibody testing and immunosuppression management in the perivaccination period. However, standardized monitoring of LT recipients at individual transplant centers and the development of a multicenter postvaccination registry to report adverse events after SARS-CoV-2 vaccination will be crucial in determining whether LT recipients are truly at increased ACR risk and how to optimize vaccination schedules during the ongoing SARS-CoV-2 pandemic.

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