RESEARCH LETTER

Durability of Antibody Response Six Months After Two-Dose SARS-CoV-2 mRNA Vaccination in Patients With Cirrhosis

Patients with cirrhosis experience increased morbidity and mortality from coronavirus disease 2019 compared to the general population.[1] As such, professional societies have recommended vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for all patients with chronic liver disease.[2,3] Patients with advanced/decompensated liver disease have evidence of immune dysfunction and attenuated humoral response to both hepatitis A virus and hepatitis B virus vaccination.[4] In healthy adults, SARS-CoV-2 antibody response persists for up to 6 months after 2-dose (D2) SARS-CoV-2 mRNA vaccination, and while studies thus far have not shown any significant difference in anti-spike antibody response among patients with cirrhosis, durability beyond 3 months postvaccination is unknown.[5–7] The aim of this study was to determine the durability of antibody levels among patients with cirrhosis up to 6 months after SARS-CoV-2 mRNA vaccination to help inform optimal timing of booster dose vaccination in this population.

Participants with cirrhosis who received D2 SARS-CoV-2 mRNA vaccination (BNT162b2 or mRNA-1273) were included. Recruitment occurred via convenience sampling through social media postings by national liver disease organizations and advocacy groups, and clinician referral. Baseline demographics and clinical characteristics were collected via electronic questionnaire. Participants <18 years of age, transplant recipients, those with prevaccination coronavirus disease 2019 diagnosis and recipients of additional vaccine doses (ie, >2 vaccine doses) were excluded. The Roche Elecsys anti-SARS-CoV-2 enzyme immunoassay, which measures circulating antibodies against the receptor-binding domain of the spike protein (range <0.4 to >250.0 U/mL with later expansion to >2500.0 U/mL in April 2021; positive >0.8 U/mL), was utilized to assess antibody response at 1, 3, and 6 months post-D2. In order to more easily compare titer response across these 2 ranges in our data set, a high-titer response was defined as ≥250.0 U/mL.[6,8,9] Associations between variables and antibody response were assessed using modified Poisson regression with a robust variance estimator. All statistical analyses were performed with $\alpha = 0.05$ using R software. The Johns Hopkins Institutional Review Board approved the study (IRB00248540), and participants provided informed consent prior to enrollment.

Forty-seven participants were included (Table 1). Thirty-two (68%) received Pfizer-BioNTech (BNT162b2) vaccination; the remainder received Moderna (mRNA-1273). Participants were predominantly female (79%) and white (89%) with a median (interquartile range) age of 60 (55–65); 53% had a history of cirrhosis-related complications/decompensation. Of the patients with autoimmune hepatitis, 3 also had primary biliary cholangitis and 2 had concomitant fatty liver disease. Of the patients on immunosuppressants, 6 were on more than one immunosuppressant at one time. All except one participant had positive antibody titer at 1-month post-D2, and all participants had positive antibody titers at 3 and 6 months, respectively. Most participants had high-titer antibody response at one (84%) and 6 months (72%) post-D2.

At 1-month post-D2, older age was associated with a lower chance of high-titer antibody response (incidence rate ratio [IRR] 0.99; 95% confidence interval [CI]: 0.97–1.00). Immunosuppressant use was associated with a 21% lower chance of having high-titer antibody response after vaccination (IRR 0.79; 95% CI: 0.56–1.11) and having a history of decompensation was associated with a 25% higher chance (IRR 1.25; 95% CI: 0.93–1.70), but these associations were not statistically significant (Table 2). At 3 months post-D2, receipt of the BNT162b2 vaccine series was associated with a 49% lower chance of having high-titer antibody response (IRR 0.51; 95% CI: 0.31–0.85) and immunosuppressant use was associated with a 35% lower chance of having high-titer antibody response (IRR 0.65; 95% CI: 0.39–1.09), but this did not reach statistical significance. At 6 months post-D2, receipt of the BNT162b2 vaccine series was associated with a 36% lower chance of having high-titer antibody response (IRR 0.64; 95% CI: 0.45–0.92). A history of decompensation was associated with a 30% lower chance of having high-titer antibody response (IRR 0.70; 95% CI: 0.49–1.02), but this did not reach statistical significance.

We performed a subgroup analysis based on vaccine type (Table A1). At 6 months post-D2, a history of liver decompensation was associated with a 41% lower chance of having high-titer antibody response among those who received the BNT162b2 vaccine series (IRR 0.59; 95% CI: 0.29–1.19). In comparison, liver decompensation was associated with a 16% lower chance of high-titer antibody response among individuals who received mRNA-1273 (IRR 0.84; 95% CI: 0.61–1.16).

Our study assessed the anti-spike antibody response 6 months after D2 SARS-CoV-2 vaccination in patients with cirrhosis. All participants had detectable antibodies at 6 months, and the majority (72%) had durable high-titer response. Study limitations include an inability to control for more covariables (eg, immunosuppressant type or dosing, liver

Table 1. Study Participant Demographic and Clinical Characteristics

Participant characteristics	Total, n = 47
Age, y	
Median (IQR)	60 (55–65)
Sex, n (%)	
Female	37 (79)
Male	10 (21)
Race, n (%)	
White	42 (89.4)
Non-white	3 (6.4)
Prefer not to answer	2 (4.3)
BMI, kg/m^2	
Median (IQR)	28.0 (25.1–32.6)
Underlying cause of liver disease, n (%)[a]	
Fatty liver disease	18 (38)
Alcoholic liver disease	3 (6)
HCV	5 (11)
HBV	1 (2)
Autoimmune hepatitis	13 (28)
Primary sclerosing cholangitis	3 (6)
Primary biliary cholangitis	5 (11)
Other	9 (19)
Complications of cirrhosis, n (%)[a]	
Jaundice	14 (30)
Gastrointestinal bleeding	9 (19)
Confusion	12 (26)
Fluid buildup in the abdomen	9 (19)
Infection of abdominal fluid	4 (9)
Liver cancer	0 (0)
None	22 (47)
On immunosuppressant medication, n (%)	
Yes	17 (36)
No	30 (64)
Type of immunosuppressant, n (%)[a]	
Corticosteroids	5 (10)
MMF	1 (2)
Azathioprine	6 (13)
Belimumab	2 (4)
Ustekinumab	1 (2)
Tofacitinib	1 (2)
Other	4 (9)
Medical conditions, n (%)[a]	
Cirrhosis	47 (100)
Autoimmune disease	21 (45)
HIV/AIDS	1 (2)
On dialysis	1 (2)
Vaccine type (manufacturer), n (%)	
BNT162b2 (Pfizer-BioNTech)	32 (68)
mRNA-1273 (Moderna)	15 (32)

Corticosteroids included prednisone and its equivalents.
Autoimmune disease was defined as having one or more of the following conditions: systemic lupus erythematosus, Sjogren's syndrome, myositis, systemic sclerosis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, inflammatory bowel disease, polyarteritis nodosa, Behcet's syndrome, polymyalgia rheumatica, temporal arteritis, eosinophilic granulomatosis polyangiitis, granulomatous polyangiitis, Henoch-Schonlein purpura, microscopic polyangiitis, and Takayasu arteritis.
BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; IQR, interquartile range; MMF, mycophenolate mofetil or mycophenolic acid; n, number of participants.
[a]Not mutually exclusive characteristics.

disease etiology) due to the small sample size, absence of a non-cirrhotic control group, lack of data on memory B-cell and cellular responses, possibility of asymptomatic infection (serial anti-nucleocapsid testing not performed), and possible selection bias resulting from convenience sampling.

Our results suggest that patients with cirrhosis who initially received the BNT162b2 vaccine series and those with a history of liver decompensation may be more likely to have a diminished antibody response at 6 months post-D2 and would benefit from booster vaccination. The difference observed in durable antibody response between mRNA vaccine types may be related to dosing or drug delivery formulation differences. A similar differential antibody response between the 2 mRNA vaccines has been demonstrated in the general population, with fewer breakthrough cases of SARS-CoV2-2 infection among those who initially received mRNA-1273 vaccination.[10] In addition, the association between decompensated cirrhosis and waning antibody titers is consistent with prior work using other vaccines and suggests a potential deficiency in memory B-cell formation or function in this patient population that warrants further investigation.[4]

R. M. HUGHES[1]
S. FREY[2]
M. TELES[2]
C. M. CONNOLLY[3]
D. L. SEGEV[4]
W. A. WERBEL[5,*]
P.-H. CHEN[6,*]

[1]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland
[2]Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland
[3]Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland
[4]Department of Surgery, NYU Grossman School of Medicine, NYU Langone Health, New York, New York
[5]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland
[6]Division of Gastroenterology and Hepatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

Correspondence:
Address correspondence to: Po-Hung Chen, MD, Division of Gastroenterology and Hepatology,

Table 2. Incidence Rate Ratios (IRRs) and 95% Confidence Intervals (CIs) for the Associations Between Various Patient Factors and High-Titer Antibody Response, Defined as Anti-SARS-CoV-2 Spike Protein Antibody Levels >250 U/mL, in Participants With Cirrhosis at 1, 3, and 6 Months After 2-Dose (D2) SARS-CoV-2 mRNA Vaccination

	1 mo post-D2		3 mo post-D2		6 mo post-D2	
Patient factors	IRR[a] (95% CI)	*P* value	IRR[a] (95% CI)	*P* value	IRR[a] (95% CI)	*P* value
Age	**0.99 (0.97–1.00)**	**.05**	0.97 (0.94–1.00)	.08	1.00 (0.99–1.02)	.68
Sex (male)	1.18 (0.79–1.76)	.43	0.87 (0.48–1.59)	.65	0.75 (0.43–1.33)	.33
Immunosuppressant use	0.79 (0.56–1.11)	.17	0.65 (0.39–1.09)	.10	0.91 (0.60–1.38)	.66
Vaccine type (BNT162b2)	1.01 (0.70–1.45)	.95	**0.51 (0.31–0.85)**	**.01**	**0.64 (0.45–0.92)**	**.01**
Decompensated cirrhosis	1.25 (0.93–1.70)	.14	1.05 (0.67–1.65)	.83	0.70 (0.49–1.02)	.06

Decompensated cirrhosis was defined as having a history of one or more of the following complications: jaundice, gastrointestinal bleeding, confusion, fluid buildup in the abdomen, infection of abdominal fluid, liver cancer.
Numbers in bold signify statistical significance with $\alpha = 0.05$.
BNT162b2, Pfizer-BioNTech mRNA vaccine; CI, confidence interval; D2, 2-dose SARS-CoV-2 mRNA vaccination; IRR, incidence rate ratio.
[a]Model adjusted for age, sex, BMI, days between vaccination and antibody testing, immunosuppressant use, vaccine type, and decompensation status. BMI, body mass index.

Johns Hopkins University School of Medicine, Baltimore, Maryland. e-mail: pchen37@jhmi.edu.

Supplementary materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2023.03.025.

References

1. Mohammed A, et al. J Clin Gastroenterol 2021;55:187–194.
2. Fix OK, et al. Hepatology 2021; 74:1049–1064.
3. Cornberg M, et al. J Hepatol 2021; 74:944–951.
4. Alukal JJ, et al. J Clin Exp Hepatol 2021;12:937–947.
5. Doria-Rose N, et al. N Engl J Med 2021;384:2259–2261.
6. Thuluvath PJ, et al. J Hepatol 2021; 75:1434–1439.
7. Ruether DF, et al. Clin Gastroenterol Hepatol 2022;20:162–172.e9.
8. Higgins V, et al. J Clin Microbiol 2021;59:e03149-20.
9. Frey S, et al. Lancet Rheumatol 2022;4:e241–e243.
10. Wang L, et al. JAMA 2022; 327:678–680.

*Co-senior authors.
Abbreviations used in this paper: **BMI, body mass index; CI, confidence interval; D2, two-dose; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; IRR, incidence rate ratio; MMF, mycophenolate mofetil or mycophenolic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.**

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Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Deidentified individual participant data will be available upon email request 3 months after publication for a period of 5 years after the publication date.

Reporting Guidelines:
Not applicable for this article type.