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JOURNAL OF HEPATOLOGY

Liver injury following SARS-CoV-2 vaccination: A multicenter case series

To the Editor:

In response to the COVID-19 pandemic, two novel mRNA-based vaccinations against the SARS-CoV-2 virus have been manufactured and distributed in an unprecedented fashion. In light of their rapid uptake, providers must remain vigilant in their monitoring of new adverse events. In early 2021, multiple providers, communicating on AST LICOP and AASLD online forums, shared strikingly similar experiences with patients who presented with liver injury following COVID-19 vaccination with no other clear precipitants. Given the pattern, we report herein on a multicenter cohort of patients with liver injury following COVID-19 vaccination. No personally identifiable information or protected health information was collected for any patient. The series was reviewed by the Northwestern University IRB and deemed not to be human subjects research.

Our cohort includes 16 total patients (Table 1) aged 25 to 74, who presented between 5 to 46 days following their first vaccine dose (Pfizer: 12, Moderna: 4). Notably, 75% of patients (12/16) presented *after* their second vaccine dose.

Six patients had a history of chronic liver disease, including 4 (#6, 10, 11, 13) with autoimmune hepatitis (AIH) in treated remission (*i.e.*, no medication changes or abnormal labs for a minimum of 6 months). Three patients had cirrhosis: 2 patients with AIH (#10 and 11) and 1 with previously treated HCV (#4).

The majority (13/16) of cases demonstrated a hepatocellular pattern of liver injury (peak alanine aminotransferase: 96 to >5,000 U/L). Of the remaining 3 cases, 1 (#4) was cholestatic and 2 (#12, 16) were mixed. Acute liver injury (ALI, defined as international normalized ratio [INR] >1.5) occurred in 3 patients (#9, 14, and 15; INR range 2.2 to 5.5); no patients developed acute liver failure.

Patient #1 was diagnosed with "new" sclerosing cholangitis via endoscopic retrograde cholangiopancreatography on this presentation; however, on chart review, he presented with drug-induced liver injury (DILI) (amoxicillin) two years earlier, at which time a magnetic resonance cholangiopancreatography showed subtle non-diagnostic biliary findings, raising the possibility of undiagnosed primary sclerosing cholangitis. At the time of presentation, the DILI was long-since resolved, and the current presentation appears to represent an ALI event in a patient with pre-existing cholangitis. Patient #2 had been prescribed a 3-day course of nitrofurantoin approximately 90 days prior to presentation. The scenario was deemed atypical for nitrofurantoin toxicity (particularly the short exposure and clinical presentation). Patients #3 and #7 used ibuprofen immediately following the second vaccine dose (2 to 3 days total, unknown total doses); patient #15 reported chronic acetaminophen use (3-4 grams for several days per week over the preceding year); and patient #16 had knee surgery 3 days prior to presentation and used alternating acetaminophen and acetaminophen-hydrocodone for a total of 4 days. None of these were deemed likely to be causative given the time frame and short exposures. No patient displayed laboratory evidence of viral hepatitis, and all patients tested negative for COVID-19 infection. While 7 of the 12 patients without previously known AIH had at least 1 positive autoimmune marker at the time of presentation, only 1 (#15) met IAIHG simplified criteria for "probable" AIH (anti-nuclear antibody 1:640, elevated IgG to 1,750 mg/dl, and biopsy "compatible" with AIH).[1]

Out of 16 patients, 10 underwent liver biopsy (Table 1). All exhibited portal inflammation (60% graded as moderate or severe). Five cases demonstrated a significant plasma cell component (of whom #10, 11, and 13 had pre-existing AIH and displayed interface activity), all of whom received prednisone. Cholestasis and bile duct reaction, though variably present, were only prominent in 1 case (#16) with severe cholestasis and minimal inflammation. Excluding patients with known cirrhosis (n = 3), significant fibrosis was not seen in any patient.

Out of 16 patients, 10 required hospitalization. In total, 6 of 16 patients required no treatment. Of the 10 who received treatment, 2 (#9, 14; both with ALI) received N-acetylcysteine infusions, and 8 (see Table 1) received steroids. Patient #1, newly diagnosed with sclerosing cholangitis, underwent biliary dilatation. Importantly, all patients recovered or were recovering from the acute event at the time of assembling our cohort.

We acknowledge that our series of patients with hepatic injury following mRNA-based COVID-19 vaccination contains retrospective and observational data without adjudication. Thus, our report is not structured to evaluate potential causality. In our patients with prior drug exposure (amoxicillin; nitrofurantoin; non-steroidal anti-inflammatory drugs, acetaminophen), the exposures were either too short or the presentations highly atypical (by laboratory data or histopathology) to be attributed solely to the medication. Thus, DILI is not readily implicated in this patient series, although it cannot be wholly excluded. We also consider unlikely direct hepatotoxicity from SARS-CoV-2 mRNA vaccines, noting the strong safety profile for delivery of lipid nanoparticle mRNA vaccines to human tissues.[2] Rather, vaccine-induced immune-mediated hepatitis is a known phenomenon,[3,4] and other autoimmune events (*e.g.*, AIH, ITP) have been reported following COVID-19 vaccination.[5,6] It is plausible that a similar mechanism is occurring here, whereby the host immune response directed against the COVID-19 spike protein triggers an aberrant, autoimmune-like hepatic condition in predisposed individuals. Many questions still remain. In particular, should patients at higher risk of hepatic autoimmunity (*e.g.*, existing AIH, post-liver transplant) undergo pre-emptive laboratory monitoring post-vaccination? Will there be safety concerns for these patients if booster doses are recommended in the future?

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Table 1. Patient characteristics.

Case	Age, sex	Liver disease history	Timing of presentation (days)[a]	Pattern of injury	Peak lab values: ALT (U/L)	ALP (U/L)	Bili (mg/dl)	INR (ratio)	Relevant work-up (medications, labs, imaging)	Biopsy findings[c]: Inflammation severity[d], location	Cellular pattern of inflammation	Cholestasis[d] and bile duct features	Fibrosis	Treatment	Recovery status
Pfizer vaccine															
1	46, M	NAFLD, prior DILI (due to amoxicillin)	10	Hep	594	197	3.9	1.3	ASMA 1:40 Other autoimmune and viral serologies negative ERCP with new severe sclerosing cholangitis	+ Portal No interface hepatitis	Mixed infiltrate	+ Mild ductular proliferation	Focal portal and peri-portal	Endoscopic biliary dilation	Recovering
2	61, F	None	34	Hep	2,331	160	3.7	1.3	Received nitrofurantoin 3 months prior ASMA 1:160, other autoimmune and viral serologies negative	+ Portal and lobular No interface hepatitis	Lymphocytes and plasma cells	None Normal bile ducts	None	Oral prednisone	Recovering
3	61, M	None	31	Hep	765	230	2.6	1.2	Ibuprofen x 3 days Autoimmune and viral serologies negative	+ Portal and lobular No interface hepatitis	Lymphocytes	None Normal bile ducts	None	None	Fully recovered
4	71, M	HCV (treated); Compensated cirrhosis	27	Chol	101	367	1.7	Unk	None performed	No biopsy performed				None	Recovering
5	74, F	Extramedullary hematopoiesis of unknown significance on prior liver biopsy	27	Hep	1,779	391	1.1	1.0	ANA 1:640, other autoimmune serologies negative Viral serologies negative	No biopsy performed				None	Fully recovered
6	73, M	AIH (treated)[b]	6	Hep	813	114	0.7	Unk	None performed	No biopsy performed				Oral prednisone	Recovering
7	25, F	None	24	Hep	635	465	2.8	1.0	Ibuprofen x 2 days ANA 1:640, ASMA 1:20; viral studies negative	No biopsy performed				None	Recovering
8	61, F	None	42	Hep	1,735	287	1.5	1.1	ANA 1:320, other autoimmune serologies negative EBV viral load 78, VZV IgM+/IgG+ Hepatic steatosis on imaging	++/+++ Portal No interface hepatitis	Mixed infiltrate	None Neutrophilic peri-cholangitis	None	Oral prednisone	Recovering
9	37, F	None	29	Hep	>5,000	144	2.8	5.5	Autoimmune and viral serologies negative	No biopsy performed				NAC infusion	Fully recovered
10	33, F	AIH (treated)[b] Compensated cirrhosis	28	Hep	173	46	2.1	1.1	None	+/++ Portal and lobular with interface hepatitis	Lymphocytes and plasma cells	None Normal bile ducts	Cirrhosis	Oral prednisone	Fully recovered
11	68, M	AIH (treated)[b] Compensated cirrhosis	19	Hep	245	55	0.9	1.1	Imaging with new diagnosis of solitary HCC	++ Portal and lobular with interface hepatitis	Mixed with plasma cells	None Normal bile ducts	Cirrhosis	Oral prednisone	Recovering
12	70, F	Prior biliary stricture after cholecystectomy	41	Mixed	96	140	0.5	Unk	None	No biopsy performed				None	Recovering

(*continued on next page*)

Table 1. (*continued*)

Case	Age, sex	Liver disease history	Timing of presentation (days)[a]	Pattern of injury	Peak lab values: ALT (U/L)	ALP (U/L)	Bili (mg/dl)	INR (ratio)	Relevant work-up (medications, labs, imaging)	Biopsy findings[c]: Inflammation severity[d], location	Cellular pattern of inflammation	Cholestasis[d] and bile duct features	Fibrosis	Treatment	Recovery status
Moderna vaccine															
13	66, F	AIH (treated)[b]	5	Hep	1,199	352	5.9	1.1	Received shingles vaccine 3 months earlier Viral serologies negative	+++ Portal and lobular with interface hepatitis and central perivenulitis	Plasma cells	None Normal bile ducts	None	Oral prednisone	Recovering
14	68, F	None	15	Hep	2,367	176	25	2.2	Autoimmune and viral serologies negative *E. Coli* UTI treated with ceftriaxone (after ALI onset)	+++ Portal and lobular Interface hepatitis not reported	Unknown	None Severe bile ductular reaction	None	IV steroids, NAC infusion	Recovering
15	59, F	None	31	Hep	869	367	14.7	2.4	Tylenol several days per week for preceding year ANA 1:640, IgG 1,750 other autoimmune serologies negative EBV VCA IgM+, IgG+ Other viral markers negative	+++ Portal and lobular No interface hepatitis	Lymphocytes	None Ductular reaction	None	IV steroids	Recovering
16	65, M	None	46	Mixed	2,664	2,522	22.3	1.2	Taking Tylenol/Norco for 4 days prior to presentation due to recent knee surgery ANA 1:1,240, ASMA 1:40, IgG normal Viral serologies negative	+ Portal No interface hepatitis	Lymphocytes	+++ Occasional bile duct injury	None	None	Recovering

AIH, autoimmune hepatitis; ALI, acute liver injury; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, anti-nuclear antibodies; ASMA, anti-smooth muscle antibodies; Bili, bilirubin; DILI, drug-induced liver injury; EBV, Epstein-Barr virus; HCC, hepatocellular carcinoma; INR, international normalized ratio; NAC, N-acetylcysteine; NAFLD, non-alcoholic fatty liver disease; UTI, urinary tract infection; VCA, viral capsid antigen.

[a]In relation to first dose of vaccine.

[b]No medication changes for over 6 months with normal preceding labs.

[c]Biopsy findings are reported based on each institution's written report. Biopsies were not independently reviewed.

[d]Severity of inflammatory infiltrate and cholestasis graded as follows: +, minimal or mild; ++, moderate; +++, severe/extensive.

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We emphasize that our intent is not to promote vaccine hesitancy. The overwhelming benefits of these and other highly efficacious vaccines in the setting of a global pandemic greatly surpass any potential risk of liver injury that may exist. We simply aim to share a clinical scenario that has been observed independently by multiple providers at various institutions, with the hope that as vaccine uptake continues to increase, our shared experience can help in early recognition, further study, and management of potential adverse events.

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Conflict of interest
The authors disclose no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
Hersh Shroff (conceptualization, methodology, visualization, writing original draft, writing review and editing). Sanjaya K. Satapathy (visualization, resources, writing review and editing). James M. Crawford (visualization, resources, writing review and editing). Nancy J. Todd (resources, writing review and editing). Lisa B. VanWagner (conceptualization, methodology, resources, supervision, visualization, writing review and editing).

Data availability statement
Data and study materials will not be made available to other researchers.

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Supplementary data
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Outcomes following liver transplant in adults with telomere biology disorders

To the Editor:

Telomeres are repetitive DNA sequences at the end of chromosomes that protect from the loss of genetic information during DNA replication.[1] When telomeres shorten, either due to inherited disorders or the normal aging process, disorders in organ systems such as the skin, bone marrow, lungs and liver can develop.[2] When premature telomere shortening is due to a genetically inherited mutation it is termed telomere biology disorder (TBD). Classic manifestations of TBD include bone marrow failure, dyskeratosis congenita (DKC), interstitial lung disease and cirrhosis.[3] There have been 3 previous reports describing liver transplantation in TBD, only one of which took

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