Letter to the Editor

JOURNAL OF HEPATOLOGY

Cases of severe acute liver injury following inactivated SARS-CoV-2 vaccination

To the Editor:

Several cases of severe acute liver injury (ALI) with features of autoimmune hepatitis after SARS-CoV-2 infection or SARS-CoV-2 vaccination have been described.[1–7] Most cases developed ALI following mRNA or viral vector-based vaccines, while only a few reports described the development of ALI after inactivated SARS-CoV-2 vaccines.[1] Recently, Wong *et al.*[8] evaluated the risk of ALI in a large cohort of vaccine recipients. They reported that the risk of ALI did not increase due to any formulation of SARS-CoV-2 vaccination. We reviewed our cohort of patients who developed ALI after inactivated SARS-CoV-2 vaccination.

We included 13 cases (female/male:7/6) with a median age of 42 (22-67) years at the time of ALI presentation (Table 1). ALI was diagnosed a median 18 (range: 2–39) days after vaccination with either the Sinopharm (n = 4), Sinovac (n = 4), Covaxin (n=4) or CanSino (n = 1) vaccines. One patient had a diagnosis of primary biliary cholangitis (PBC). None of the individuals were taking any medication prior to the onset of liver injury. Aminotransferase levels had been checked in eight (61%) individuals a median of 80 (25-210) days prior to the onset of liver injury and were normal in all. Nine (70%) cases developed ALI after the first vaccine dose, while four (30%) were diagnosed after the second dose. A hepatocellular pattern of injury was noted in 12 and a cholestatic pattern in one case.

Anti-nuclear antibody was positive in eight cases, and three cases showed seropositivity for anti-smooth muscle antibody. The serum IgG levels were measured in 12 cases and were high in six of these. Liver biopsy was performed in three cases. Six (46%) cases reached probable or definitive autoimmune hepatitis according to simplified criteria. Most cases (11/13) had features of grade 1-2 (mild-moderate) liver injury, one had grade 3 (severe) and another case had grade 4 (fatal) liver injury.

Corticosteroid therapy was given to five patients and could be successfully withdrawn in four of them. The median time from ALI to complete biochemical resolution was 39 days (20-120) in treated and untreated patients, and no relapse was observed after a median 265 (20-450) days follow-up.

Wong *et al.*.[8] did not report severe or fatal cases of ALI following SARS-CoV-2 vaccination in their study population. In our data, 15% (2/13) of cases had grade 3-4 liver injury. One of them responded to corticosteroid therapy, while another patient (not treated with corticosteroid) who had a PBC diagnosis progressed to decompensated liver failure (developed ascites and encephalopathy) 20 days after the second dose of Sinopharm. The patient underwent liver transplantation and is alive after 60 days of follow-up. To the best of our knowledge, this is the second patient who underwent liver transplantation following vaccine-induced liver injury.[9] Importantly, our case series contains observational data and does not suggest increased risk of ALI following SARS-CoV-2 vaccination. The association of SARS-CoV-2 vaccination and risk of ALI can be better postulated with case control studies as was done by Wong *et al.*[8]

Table 1. Characteristics of the study population.

Characteristics	
Patient number	N = 13
Age (years)	42 (22-67)
Sex, female, n (%)	7 (54)
Pre-existing liver disease, n (%)	1 (8)
Symptoms at liver injury onset, n (%)	11(85)
Peak ALT xULN	17.2 (2.2-56.6)
Peak AST xULN	10.8 (1.4-26)
Peak ALP xULN	1 (0.6-2.4)
Peak total bilirubin xULN	1.2 (0.4-27.6)
INR	1.1 (0.8-4.7)
Hepatocellular liver injury, n (%)	12(92)
IgG xUNL	1.04 (0.60-1.51)
ANA positivity, n (%)	56 (67.5)
SMA positivity, n (%)	15 (18.1)
Grade of liver injury (1-2)/(3-4), n (%)	11(85)/2(15)
Corticosteroid response, n (%)	5 (100)
Liver transplantation, n (%)	1 (8)

Values reported as median (range).
ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, anti-nuclear antibody; AST, aspartate aminotransferase; INR, international normalized ratio; SMA, smooth muscle antibody.

The authors do not discourage SARS-CoV-2 vaccination. In our data, most patients (12/13) showed resolution of liver injury with or without therapy and no patient relapsed during follow-up. This outcome suggests that SARS-CoV-2 vaccine-induced ALI is usually transient. Similar results were also reported in other studies.[1,5] Vaccination has significantly reduced the risk of severe COVID-19 and mortality during the pandemic.[3,10] Compared to the billions of people vaccinated across the World, only a fraction of individuals may develop vaccine-induced ALI. Through this series, we only aim to increase the awareness of post-vaccination ALI and suggest close follow-up of individuals who present with ALI following SARS-CoV-2 vaccination.

Anand V. Kulkarni[1]
Margarita Anders[2]
Leyla Nazal[3]
Ezequiel Ridruejo[4,5,6]
Cumali Efe[7,*]

[1]*Department of Hepatology and Liver Transplantation, Asian Institute of Gastroenterology Hospitals, Gachibowli, Hyderabad, India, 500032*
[2]*Hepatology and Liver Transplant Unit, Hospital Alemán, Ciudad Autónoma de Buenos Aires, Argentina*

[3]*Gastroenterology and Hepatology Unit, Clínica Las Condes, Santiago de Chile, Chile*
[4]*Latin American Liver Research Educational and Awareness Network (LALREAN), Pilar, Argentina*
[5]*Hepatology and Liver Transplant Unit, Hospital Universitario Austral, Pilar, Argentina*
[6]*Hepatology Section, Department of Medicine, Centro de Educación Médica e Investigaciones Clínicas, CEMIC, Ciudad Autónoma de Buenos Aires, Argentina*
[7]*Department of Gastroenterology, Harran University Hospital, Şanlıurfa, Turkey*

[*]Corresponding author. Address: Department of Gastroenterology, Harran University Hospital, Şanlıurfa, Turkey.
E-mail address: scumaliefe@gmail.com (C. Efe)

Received 5 October 2022; Received in revised form 24 October 2022; Accepted 25 October 2022; Available online xxx
https://doi.org/10.1016/j.jhep.2022.10.026

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.
Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

CE, and AVK conceptualized the study. CE, LN, AVK, MA SW and ER contributed data and approved final manuscript.

Data availability statement

All relevant data that support the findings are presented in the manuscript.

Acknowledgements

We acknowledge the following individuals for assistance in contributing cases: Ramazan Idilman (Ankara University Medical Faculty, Ankara, Turkey); Emine Kübra Dindar-Demiray (Bitlis Tatvan State Hospital, Bitlis, Turkey), Fatima Higuera-de la Tijera (Hospital General de México, Mexico City, Mexico).

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.10.026.

References

Author names in bold designate shared first authorship.

[1] Efe C, Kulkarni AV, Terziroli Beretta-Piccoli B, Magro B, Stättermayer A, Cengiz M, et al. Hepatology 2022. https://doi.org/10.1002/hep.32572. 10.1002/hep.32572.

[2] **Efe C**, **Dhanasekaran R**, Lammert C, Ebik B, Higuera-de la Tijera F, Aloman C, et al. Outcome of COVID-19 in patients with autoimmune hepatitis: an international multicenter study. Hepatology 2022;76:1576–1586.

[3] **Marjot T**, **Eberhardt CS**, **Boettler T**, Belli LS, Berenguer M, Buti M, et al. Impact of COVID-19 on the liver and on the care of patients with chronic liver disease, hepatobiliary cancer, and liver transplantation: an updated EASL position paper. J Hepatol 2022;77:1161–1197.

[4] Kabaçam G, Wahlin S, Efe C. Autoimmune hepatitis triggered by COVID-19: a report of two cases. Liver Int 2021;41:2527–2528.

[5] **Codoni G**, **Kirchner T**, Engel B, Villamil AM, Efe C, Stättermayer AF, et al. Histological and serological features of acute liver injury after SARS-CoV-2 vaccination. JHEP Rep 2022. https://doi.org/10.1016/j.jhepr.2022.100605.

[6] Kulkarni AV, Vasireddy S, Sharma M, Reddy ND, Padaki NR. COVID-19 masquerading as autoimmune hepatitis (AIH) flare-the first report. J Clin Exp Hepatol 2022;12:241–243.

[7] Patel AH, Amin R, Lalos AT. Acute liver injury and IgG4-related autoimmune pancreatitis following mRNA-based COVID-19 vaccination. Hepatol Forum 2022;3:97–99. https://doi.org/10.14744/hf.2022.2022.0019.

[8] **Wong CKH**, **Mak LY**, Au ICH, Lai FTT, Li X, Wan EYF, et al. Risk of acute liver injury following the mRNA (BNT162b2) and inactivated (CoronaVac) COVID-19 vaccines. J Hepatol 2022. https://doi.org/10.1016/j.jhep.2022.06.032.

[9] Efe C, Harputluoğlu M, Soylu NK, Yilmaz S. Letter to the editor: liver transplantation following severe acute respiratory syndrome-coronavirus-2 vaccination-induced liver failure. Hepatology 2022;75:1669–1671.

[10] **Efe C**, **Taşçılar K**, Gerussi A, Bolis F, Lammert C, Ebik B, et al. SARS-CoV-2 vaccination and risk of severe COVID-19 outcomes in patients with autoimmune hepatitis. J Autoimmun 2022;132:102906.