Financial support
The study did not receive any external funding.

Conflicts 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
VM, FD, SB, MS: conception of the study, analysis and interpretation of the data, draft of the manuscript. All other members of the Demosthenes group facilitated the study or took care of the reported patients.

Demosthenes research group
François Depret,[1] Samir Bouam,[2] Michaël Schwarzinger,[3] Hélène Fontaine,[4] Marion Corouge,[4] Anaïs Vallet Pichard,[4] Clémence Hollande,[4] Philippe Sogni,[4] Stanislas Pol,[4] Vincent Mallet[4]

[1]AP-HP.Nord Université de Paris, Groupe Hospitalier St-Louis-Lariboisière, DMU Parabol, Département d'Anesthésie Réanimation et Centre de Traitement des Brûlés, Paris, France; FHU Promice Paris France; INI-CRCT, Nancy, France ; [2]AP-HP.Centre Université de Paris, Groupe Hospitalier Cochin Port Royal, DMU PRIME, Unité d'Information Médicale, Paris, France ; [3]Service de soutien méthodologique et d'innovation en prévention (SSMIP), CHU de Bordeaux; 33000 Bordeaux, France; University of Bordeaux, Inserm UMR 1219-Bordeaux Population Health, 33000 Bordeaux, France ; [4]AP-HP.Centre Université de Paris, Groupe Hospitalier Cochin Port Royal, DMU Cancérologie et spécialités médico-chirurgicales, Service d'Hépatologie, Paris, France

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.11.020.

References
[1] Giabicani M, Le Menestrel A, Roux O, Rautou PE, Weiss E, COVID-ICU study group. Focus on the decisions to forego life-sustaining therapies during ICU stay of patients with cirrhosis and COVID-19: a case control study from the prospective COVID-ICU database. J Hepatol 2022;76(3):742–744.
[2] Mallet V, Beeker N, Bouam S, Sogni P, Pol S, Demosthenes research group. Prognosis of French COVID-19 patients with chronic liver disease: a national retrospective cohort study for 2020. J Hepatol 2021;75(4):848–855.
[3] COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med 2021;47(1):60–73.

François Depret[1,2,3,4]
Samir Bouam[5]
Michaël Schwarzinger[6,7]
Vincent Mallet[1,8,*] for the Demosthenes research group
[1]*Université de Paris, F-75006 Paris, France*
[2]*AP-HP.Nord Université de Paris, Groupe Hospitalier St-Louis-Lariboisière, DMU Parabol, Département d'Anesthésie Réanimation et Centre de Traitement des Brûlés, Paris, France*
[3]*FHU Promice, Paris, France*
[4]*INI-CRCT, Nancy, France*
[5]*AP-HP.Centre, Groupe Hospitalier Cochin Port Royal, DMU PRIME, Service d'Information Médicale, Paris, France*
[6]*Service de soutien méthodologique et d'innovation en prévention (SSMIP), CHU de Bordeaux, 33000 Bordeaux, France*
[7]*Université de Bordeaux, Inserm UMR 1219-Bordeaux Population Health, 33000 Bordeaux, France*
[8]*AP-HP.Centre, Groupe Hospitalier Cochin Port Royal, DMU Cancérologie et spécialités médico-chirurgicales, Service d'Hépatologie, Paris, France*
[*]Corresponding author. Address: 27 rue du Faubourg Saint Jacques 75014, Paris. France.
E-mail address: vincent.mallet@aphp.fr (V. Mallet)

Immune-mediated hepatitis with the Moderna vaccine, no longer a coincidence but confirmed

To the Editor:

We have read with interest the recent cases suggesting the possibility of vaccine-induced immune-mediated hepatitis with Pfizer-BioNTech and Moderna mRNA-1273 vaccines for the SARS-CoV-2 virus.[1–7] However, as the cohort of vaccinated individuals against COVID-19 increases, the previously reported cases could not exclude a coincidental development of autoimmune hepatitis, which has an incidence of 3/100,000 population per year.[8] Our case demonstrates conclusive evidence of vaccine-induced immune-mediated hepatitis with a rapid onset of liver injury after the first Moderna dose, which on re-exposure led to acute severe autoimmune hepatitis.

Case description
A 47-year-old Caucasian man, previously completely well, received his 1st Moderna vaccine dose on the 26 April 2021. He noted malaise and jaundice 3 days after. Investigations on the 30th April showed serum bilirubin 190 μmol/L (normal 0-20), alanine aminotransferase (ALT) 1,048 U/L (normal 10-49), alkaline phosphatase (ALP) 229 U/L (normal 30-130), albumin 41 g/L (normal 35-50). Blood count, renal function and international normalized ratio (INR) were normal. Liver function tests (LFTs) last checked 4 years previously were normal. He denied

Keywords: Immune-mediated liver damage; drug induced liver injury; autoimmune hepatitis; covid-19.
Received 13 September 2021; received in revised form 22 September 2021; accepted 26 September 2021; available online 5 October 2021
https://doi.org/10.1016/j.jhep.2021.09.031

paracetamol use and reported minimal alcohol intake. Ultrasound scan, CT thorax, abdomen and pelvis and MRI pancreas performed to exclude malignancy, showed no significant findings. Serum IgG was raised at 25.1 g/L (normal 6-16), IgM 2.2 g/L (0.5-2) and serum was positive for anti-nuclear antibody. Serological tests for HAV, HBV, HCV, HEV, EBV and CMV were negative.

His jaundice faded and LFTs improved: bilirubin falling on 25th June to 69 μmol/L and ALT to 332 U/L. The patient received his 2nd Moderna vaccine dose on the 6 July 2021 (despite reporting the jaundice to the vaccination centre) and the jaundice returned a few days after. Blood tests on 20th July found bilirubin 355 μmol/L, ALT 1,084 U/L and a raised prothrombin time (PT) of 18.4 seconds. After liver biopsy on the 21st July 2021, prednisolone 40 mg/day was commenced and he was transferred to our service.

On examination, he was alert, deeply jaundiced, with hepatomegaly but no ascites. Repeat abdominal ultrasound showed a mildly fatty liver, patent portal and hepatic vein flow, with no ascites. Review of the liver biopsy showed acute active hepatitis: widespread areas of bridging necrosis, marked interface hepatitis, lymphoplasmatic inflammation including eosinophils, ballooned hepatocytes, multi-nucleated giant cells, and emperipolesis (Fig.1). There was minimal fibrosis, Ishak stage 1. The pattern of injury on histology was consistent with acute hepatitis, with features of autoimmune hepatitis or possible drug-induced liver injury (DILI), triggering an autoimmune-like hepatitis.

Prednisolone 40 mg/day was continued and LFTs improved (Fig. 1). He was discharged on prednisolone and on follow-up, blood tests continue to improve, and PT normalised within 2 weeks.

Discussion

This case illustrates immune-mediated hepatitis secondary to the Moderna vaccine, which on inadvertent re-exposure led to worsening liver injury with deranged synthetic function. This occurred in a well man with no other medical problems. The onset of jaundice associated with the mRNA vaccine was unusually rapid. This was also illustrated in the other cases where symptoms developed over a median of 7 days (range 4-35). Latency is usually longer in other causes of DILI, but can vary depending on mode of injury.

The mRNA vaccine pathway triggers pro-inflammatory cytokines including interferon and cross-reactivity has been illustrated between the antibodies against the spike protein and self-antigens.[9,10]

Seven cases of suspected immune-mediated hepatitis have been reported with SARS-2-COV mRNA vaccines (3 with Pfizer and 4 with Moderna).[1–7] Liver histology was assessed in every case and findings were similar to ours, indicating acute hepatitis with interface hepatitis, lymphoplasmacytic infiltrate and absence of fibrosis. Eosinophils as part of the infiltrate, which can be noted in DILI were present in 3 cases. All 7 patients responded well to steroids (n = 5 prednisolone, n = 1 budesonide and n = 1 methylprednisolone). In 3 cases there were features suggesting coincidental autoimmune hepatitis: a 35-year-old lady in her third trimester of pregnancy with positive double-stranded DNA, an 80-year-old lady with a history of autoimmune conditions and a 41-year-old lady with strongly positive auto-antibody panel after both doses of vaccination. In the other 4 cases, a raised IgG, with at least 1 positive antibody was noted in 3 cases.[4–7]

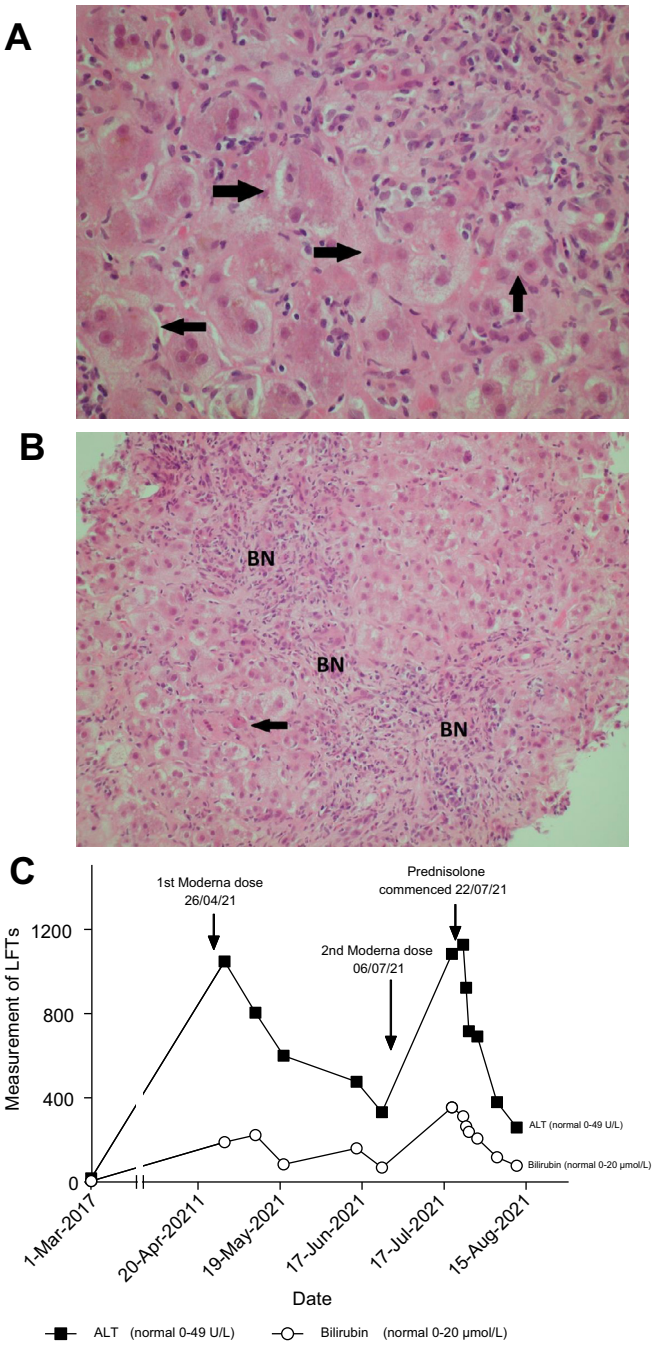

Fig. 1. Histological findings and biochemical findings. H&E-stained section of liver biopsy indicates acute hepatitis. (A) The parenchymal hepatocytes are arranged into rosette forms (marked with arrows) with cholestasis. (B) BN from hepatocyte loss, some by apoptosis (arrow). (C) Diagram showing trend of bilirubin and ALT following Moderna vaccine dose 1 and 2 with response to prednisolone. ALT, alanine aminotransferase; BN, bridging necrosis. (This figure appears in color on the web.)

This case has confirmed immune-mediated hepatitis secondary to the Moderna vaccine, which on inadvertent re-exposure led to acute severe hepatitis. Treatment with corticosteroid therapy appears to be favourable. We wish to highlight

that immune-mediated reactions from the SARS-CoV-2 mRNA vaccines are very rare and during the COVID pandemic, the vaccination programme continues to be crucial. We report this case to encourage vigilance for drug-induced reactions and to raise awareness to vaccination centres to incorporate it into their routine checks before administering second doses. Long-term follow up of identified individuals will be essential in determining the prognosis of this immune-mediated liver injury.

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
DG and AAJ conceptualised the work. GT wrote the initial draft and all authors contributed to and approved the final manuscript.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.09.031.

References
[1] Bril F, Al Diffalha S, Dean M, Fettig DM, et al. Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: causality or casualty? J Hepatol 2021;75(1):222–224.
[2] Rocco A, Sgamato C, Compare D, Nardone G, et al. Autoimmune hepatitis following SARS-CoV-2 vaccine: may not be a casualty. J Hepatol 2021;75(3):728–729.
[3] Londono MC, Gratacos-Gines J, Saez-Penataro J. Another case of autoimmune hepatitis after SARS-CoV-2 vaccination. Still casualty? J Hepatol 2021. https://doi.org/10.1016/j.jhep.2021.06.004.
[4] Ghielmetti M, Schaufelberger HD, Mieli-Vergani G, Cerny A, et al. Acute autoimmune-like hepatitis with atypical anti-mitochondrial antibody after mRNA COVID-19 vaccination: a novel clinical entity? J Autoimmun 2021;123:102706.
[5] McShane C, Kiat C, Rigby J, Crosbie O, et al. The mRNA COVID-19 vaccine - a rare trigger of Autoimmune Hepatitis? J Hepatol 2021. S0168-8278(21)01896-1.
[6] Tan CK, Wong YJ, Wang LM, Ang TL, et al. Autoimmune hepatitis following COVID-19 Vaccination: true causality or mere association? J Hepatol 2021;18. S0168-8278(21)00424-4.
[7] Lodato F, Larocca A, D'Errico A, et al. An unusual case of cholestatic hepatitis after m-RNABNT162b2 (Comirnaty) SARS-CoV-2 vaccine: coincidence, autoimmunity or drug related liver injury? J Hepatol 2021. https://doi.org/10.1016/j.jhep.2021.07.005.
[8] Grønbaek L, Otete H, Ban L, Crooks C, et al. Incidence, prevalence and mortality of autoimmune hepatitis in England 1997-2015. A population-based cohort study. Liver Int 2020;40(7):1634–1644.
[9] Vojdani A, Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. Clin Immunol 2020;217:108480.
[10] Teijaro JR, Farber DL. COVID-19 vaccines: modes of immune activation and future challenges. Nat Rev Immunol 2021;21:195–197.

Gloria Shwe Zin Tun*
Dermot Gleeson
Amer Al-Joudeh
Asha Dube
Department of Gastroenterology and Hepatology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom
*Corresponding author. Address: Department of Gastroenterology and Hepatology, Sheffield Teaching Hospitals NHS Foundation Trust, Herries Rd, Sheffield, S5 7AU United Kingdom; Tel.: 0114 2715414, fax: 0114 3052843.
E-mail address: g.tun@nhs.net (G.S. Zin Tun)

Comment on "Synthetic human *ABCB4* mRNA therapy rescues severe liver disease phenotype in a BALB/c.*Abcb4*$^{-/-}$ mouse model of PFIC3"

To the Editor:

We have read with interest the paper by Wei *et al.*[1] and we thank the authors for their reference to our 2019 study on adeno-associated virus (AAV)-mediated gene therapy correction of progressive familial intrahepatic cholestasis type 3 (PFIC3) in a clinically relevant mouse model.[2] Their results utilizing lipid nanoparticles (LNP) to deliver functional human *ABCB4* mRNA to hepatocytes of BALB/c.*Abcb4*$^{-/-}$ mice and the therapeutic effect achieved in this severe PFIC3 mouse model with a high degree of fibrosis were quite remarkable. However, they framed their conclusions with respect to our previous study based on improper interpretations of several key aspects of our results. First, they did not consider our results when claiming they identified for the first time a 'minimum' of clinically meaningful restoration of hepatic phosphatidylcholine (PC) output, which was 10-42% of normal levels, *i.e. de novo* phenotypic ABCB4 enzymatic activity that resulted in a therapeutic effect. They stated that our results showed that a bile PC restoration of 70–100% was necessary for a therapeutic effect. In reality, our data pinpointed a threshold of around 4,000 μM of PC concentration in bile, which corresponded to 12–13% of the levels we measured in healthy wild-type mice (Fig. 1), which was clearly shown in our paper.[2] This is substantially less than the 70-100% they claimed we reported and actually shows

Keywords: Genetic therapy; Cholestasis; progressive familial intrahepatic 3; Dependovirus; Liver Cirrhosis; Child; Bile; Phospholipids.
Received 20 September 2021; received in revised form 28 September 2021; accepted 28 September 2021; available online 6 October 2021
https://doi.org/10.1016/j.jhep.2021.09.033