Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

liver. No thrombus was identified in the portal, splenic, hepatic, or superior mesenteric veins. An MRI cholangiogram revealed mild peri-portal oedema, no biliary dilatation, and smooth bile duct contour with no evidence of stricturing.

During ongoing close follow-up, he developed pruritus and had a corresponding worsening of his liver function tests (with a bilirubin of 38 μmol/L, ALT of 2550 U/L, and AST of 943 U/L). He was commenced on 60 mg of prednisolone daily, admitted to hospital, and had a liver biopsy 3 days after commencing the corticosteroids. His biopsy was significant for interface hepatitis with a mixed, predominantly lymphocytic, inflammatory cell infiltrate without significant fibrosis. Copper and iron stains were negative. These findings are consistent with an acute hepatitis of autoimmune aetiology. The post-biopsy pre-treatment Revised Original Score for Autoimmune Hepatitis[4] is 15 (supporting a *probable* diagnosis of AIH). His prednisolone has been weaned over the following month and is now down to 20 mg/day, with an ALT of 163 U/L and bilirubin of 7 μmol/L (Fig. 1) after 24 days of corticosteroid therapy.

In contrast to the communique published by Bril *et al.*,[1] our patient received the Oxford-AstraZeneca vaccine and did not have any apparent confounding factors such as pregnancy. This case supports the notion of COVID-19 vaccine-triggered autoimmune phenomena irrespective of the vaccine's mechanism of action, though this is the first report of an adenovirus-based vaccine precipitating AIH. Similar to the previously described case by Bril *et al.*,[1] causation cannot be definitively proven and it is possible that other factors, including drugs or toxins, may have contributed to the presentation. In this case, however, the patient is a practicing physician with excellent health literacy and we feel it is unlikely that other potential aetiologies were missed on history.

The case of this 36-year-old previously well man developing apparent AIH precipitated by a COVID 19-vaccine is another salient reminder to be vigilant of the rapidly changing landscape of potentially rare complications associated with novel vaccine agents and mass immunisation programs worldwide.

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Authors' contributions
DCC provided patient care as well as co-wrote the original manuscript and edited the final submission; DS co-wrote the original manuscript and edited the final submission; EF provided patient care, assisted with conceptualisation, and edited the final submission; WK provided patient care, assisted with conceptualisation, and edited the final submission; SKR provided patient care, assisted with conceptualisation, and edited the final submission.

Supplementary data
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References
[1] Bril F, Al Diffalha S, Dean M, Fettig DM. Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: causality or casualty? J Hepatol 2021;75:222–224. https://doi.org/10.1016/j.jhep.2021.04.003.
[2] Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med April 15 2021;384:1412–1423. https://doi.org/10.1056/NEJMoa2101765.
[3] Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med April 9 2021. https://doi.org/10.1056/NEJMoa2104882.
[4] Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999;31(5):929–938. https://doi.org/10.1016/s0168-8278(99)80297-9.

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Autoimmune hepatitis following COVID-19 vaccination: True causality or mere association?

To the Editor:
The COVID-19 pandemic is still raging across the world and vaccination is expected to lead us out of this pandemic. Although the efficacy of the vaccines is beyond doubt, as many vaccines were granted expedited approval, safety still remains a concern.[1] In light of this, we read with great interest a recent article by Bril *et. al.*[2] They described a case of autoimmune hepatitis (AIH) possibly triggered by COVID-19 vaccination. However, as the patient was 3-months post-partum a true causal relationship is difficult to determine.[3] We hereby describe a case of severe AIH

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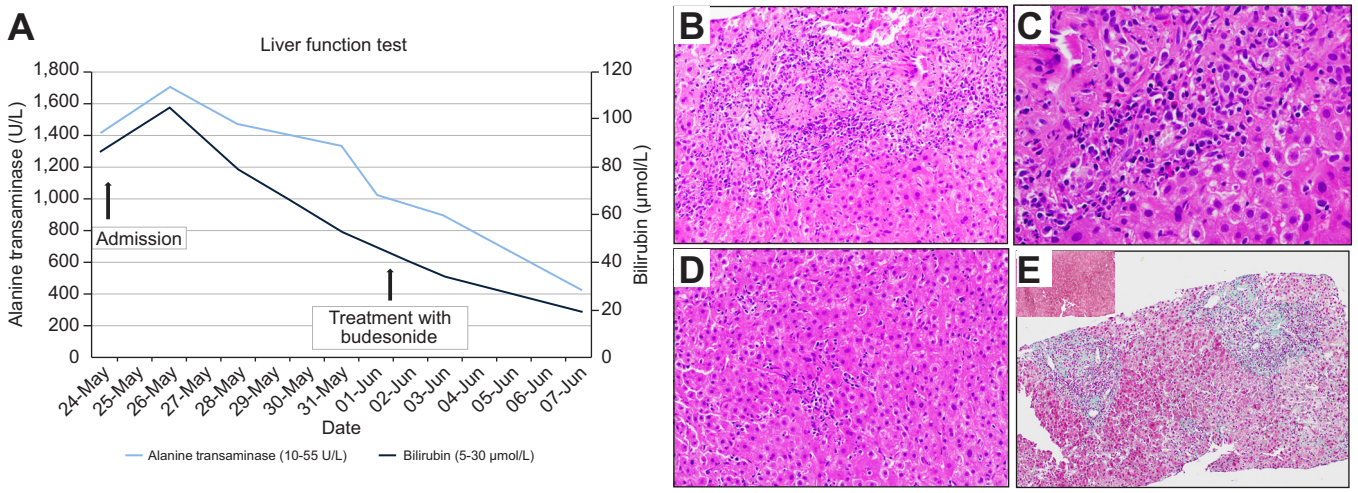

Fig. 1. Liver function test and histology of liver biopsy. (A) Graph showing the trend of bilirubin (μmol/L) and alanine aminotransferase (U/L) before and after starting treatment with budesonide on 1-June 2021. (B) H&E-stained section of liver biopsy at 200x magnification showing a portal tract with portal inflammation and interface damage. (C) Higher magnification (400x) of the portal and interface inflammatory cells showing aggregates of plasma cells, lymphocytes and few eosinophils. (D) Within the liver parenchyma (200x magnification), there is lobulitis with clusters of plasma cells, rosette formation and apoptotic hepatocytes. (E) The Masson's trichrome stain (100x magnification) showed pale green staining of the portal regions with a lack of elastic fibres seen on orcein stain (inset, 100x magnification), consistent with recent young fibrosis. Elastic fibres appear black on orcein stains and are usually absent in normal portal tracts. Old fibrosis type collagen contains elastic fibres and is a useful indicator of chronicity on histology. (This figure appears in color on the web.)

in a pre-morbidly well patient after the first dose of Moderna-COVID-19 vaccine (mRNA-1273).

A 56-year-old woman received her first dose of Moderna-COVID-19 vaccine (mRNA-1273) on 14-April 2021. She developed intense malaise and flu-like symptoms the next day, owing to which she later decided against receiving the recommended second dose. Six weeks after vaccination, she presented with a 1-week history of jaundice, feeling unwell and persistent anorexia. Apart from her regular medication (rosuvastatin 10 mg daily) started 9 years ago, she was not on any other prescription or traditional medication/supplements. Prior to admission, her last liver function test was performed in 2019 and was normal. On the day of presentation, her physical examination was normal except for scleral icterus. The initial laboratory studies showed that she had hepatocellular injury (albumin 46 g/L, bilirubin 102 μmol/L, alkaline phosphatase 298 U/L, alanine aminotransferase [ALT] 1,701 U/L, aspartate aminotransferase 1,124 U/L, international normalized ratio 1.0) fulfilling Hy's law.[4] Acute viral hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis E, cytomegalovirus, Epstein-Barr virus, herpes simplex virus) was excluded and cross-sectional abdominal imaging was unremarkable. Antinuclear antibody and anti-smooth muscle antibody were positive and serum IgG level was raised (32.6 G/L). The trend in bilirubin and ALT levels is illustrated in Fig. 1A. Liver biopsy demonstrated portal inflammation with interface hepatitis, accompanied by conspicuous lobular inflammation with the presence of plasma cell aggregates, rosette formation and apoptotic hepatocytes (Fig. 1B–D). The histological features are in-keeping with an AIH-type pattern. Eosinophils were also identified, raising the possibility of drug association. Early young fibrosis is noted in the portal regions and would be compatible with recent subacute injury (Fig. 1E).

The details of lab work are presented in Table S1 and S2. The pre-treatment revised original AIH score[5] was 16. The patient was started on budesonide which led to rapid clinical and biochemical improvement (Fig. 1A).

COVID-19 infection is not known to impact outcomes of patients with AIH, but little is known about the relationship between COVID-19 vaccines and AIH.[6] Drug-induced AIH (DI-AIH) is often a diagnostic challenge.[7,8] Features favouring DI-AIH include history of recent drug exposure, absence of advanced fibrosis on liver histology and lack of relapse after stopping immunosuppressants.[5,6] While our patient is still undergoing steroid therapy, other features are suggestive of DI-AIH. However, a few considerations require particular attention. Although statins are well known to cause DI-AIH, the median latency in statin-induced AIH is around 150 days.[9] Given the temporal sequence, results of biochemistry, immunological assays (Table S1) and typical histological changes on liver biopsy, diagnosis of DI-AIH due to the COVID19 vaccine is most plausible. While DI-AIH is rare,[10] the diagnosis of vaccine-related DI-AIH carries 2 important clinical implications. First, the re-exposure to a second dose of COVID-19 vaccine might trigger a fulminant AIH flare and second, prolonged immunosuppression may not be required. Thus, an accurate diagnosis and being aware of this rare complication of COVID mRNA vaccines is vital. DI-AIH after COVID-19 vaccination has rarely been reported to date (2), which might be due to either minimal awareness of this condition or the fact that patients without icteric disease do not usually present to hospitals.

Our report differs from that of Bril *et. al.*[2] in a few important domains. Firstly, our patient is not post-partum, which could be seen as a confounder[3] emphasizing that DI-AIH post COVID-19 vaccination might have been a causal relationship rather than just an association. Secondly, our patient was inoculated with the Moderna-COVID-19 vaccine (mRNA-1273) and not the Pfizer-BioNTech vaccine. However, both are mRNA vaccines. The mechanism by which the mRNA vaccines could cause DI-AIH is explained by Bril *et al.* in their report[2] and we hold the same view

that molecular mimicry might be the potential mechanism underlying these mRNA vaccine-induced autoimmune conditions.

In conclusion, we would like to emphasize that clinicians need to remain vigilant and should consider DI-AIH secondary to mRNA vaccines in patients with similar presentation. However, this rare complication of the Moderna-COVID-19 vaccine (mRNA-1273) should not deter people from getting vaccinated.

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References
Author names in bold designate shared co-first authorship

[1] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384(5):403–416.
[2] Bril F, Al Diffalha S, Dean M, Fettig DM. Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: causality or casualty? J Hepatol 2021;75:222–224.
[3] Capecchi PL, Lazzerini PE, Brillanti S. Comment to the letter of Bril F et al. "Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) Vaccine: causality or casualty?". J Hepatol 2021;75:994–995.
[4] Robles-Diaz M, Lucena MI, Kaplowitz N, Stephens C, Medina-Cáliz I, González-Jimenez A, et al. Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. Gastroenterology 2014;147(1):109–118.
[5] Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999;31:929–938.
[6] **Marjot T**, **Buescher G**, **Sebode M**, Barnes E, Barritt AS, Armstrong MJ, et al. SARS-CoV-2 infection in patients with autoimmune hepatitis. J Hepatol 2021;74(6):1335–1343.
[7] Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American association for the study of liver diseases. Hepatology 2020 Aug;72(2):671–722.
[8] European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; clinical practice guideline panel: chair; panel members; EASL governing board representative: EASL clinical practice guidelines: drug-induced liver injury. J Hepatol 2019 Jun;70(6):1222–1261.
[9] Russo MW, Hoofnagle JH, Gu J, Fontana RJ, Barnhart H, Kleiner DE, et al. Spectrum of statin hepatotoxicity: experience of the drug-induced liver injury network. Hepatology 2014;60(2):679–686.
[10] Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, et al. Diagnosis and management of autoimmune hepatitis. Hepatology 2010;51:2193–2213.

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The mRNA COVID-19 vaccine – A rare trigger of autoimmune hepatitis?

To the Editor:

We read with interest the letters "Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) Vaccine: Causality or casualty?" by Bril *et al.*[1] and "Autoimmune hepatitis following SARS-CoV-2 vaccine: May not be a casuality" by Rocco *et al.*[2] which highlight the hypothesis that COVID-19 mRNA-based vaccines might increase the risk of developing autoimmune diseases. There are growing reports of autoimmune diseases developing after SARS-CoV-2 infection, including Guillain-Barré syndrome and primary biliary cholangitis.[3] It is speculated that SARS-CoV-2 can disturb self-tolerance and trigger autoimmune responses through cross-reactivity with host cells and that the COVID-19 mRNA vaccines may trigger the same response.[4,5]

We report a further case of autoimmune hepatitis (AIH) following COVID-19 mRNA vaccination. Our patient is a 71-year-old Caucasian female. Background history was significant for cholecystectomy 20 years previously, left total hip replacement and osteoarthritis of the knees. There were no risk factors for

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