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Liver, Pancreas and Biliary Tract

Clinical update on risks and efficacy of anti-SARS-CoV-2 vaccines in patients with autoimmune hepatitis and summary of reports on post-vaccination liver injury

Ana Lleo^{a,b,*}, Nora Cazzagon^c, Cristina Rigamonti^d, Giuseppe Cabibbo^e, Quirino Lai^f, Luigi Muratori^{g,h}, Marco Carboneⁱ, on behalf of the Italian Association for the Study of the Liver

^a Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy

^b Internal Medicine and Hepatology Unit, Department of Gastroenterology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

^c Gastroenterology Unit, Department of Surgery, Oncology, and Gastroenterology, University of Padova, Padova, Italy

^d Department of Translational Medicine, Università del Piemonte Orientale and Division of Internal Medicine, Azienda Ospedaliero-Universitaria Maggiore della Carità, Novara, Italy

^e Section of Gastroenterology and Hepatology, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, PROMISE, University of Palermo, Palermo, Italy

^f Unità di Chirurgia Generale e Trapianti d'Organo, Dipartimento di Chirurgia Generale e Specialistica, Sapienza Università di Roma, Azienda Ospedaliero-Universitaria Policlinico Umberto I di Roma, Italy

^g Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

^h Center for the Study and Treatment of Autoimmune Diseases of the Liver and Biliary System, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

ⁱ Division of Gastroenterology, Center for Autoimmune Liver Diseases, Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

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ABSTRACT

Patients with liver diseases, especially those with cirrhosis, have an increased mortality risk when infected by SARS-CoV-2 and therefore anti-SARS-CoV-2 vaccine has been recommended by leading Scientific Associations for all patients with chronic liver diseases. However, previous reports have shown a reduced antibody response following the full course of vaccination in immunosuppressed patients, including liver transplant recipients and several rheumatic diseases.

This document, drafted by an expert panel of hepatologists appointed by the Italian Association for the Study of the Liver (AISF), aims to present the updated scientific data on the safety and efficacy of anti-SARS-CoV-2 mRNA vaccines in patients with autoimmune hepatitis (AIH). Furthermore, given the recent reports of sporadic cases of AIH-like cases following anti-SARS-CoV-2 mRNA vaccines, we summarize available data. Finally, we provide *experts recommendations* based on the limited data available.

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1. 2022 AISF recommendation on anti-SARS-CoV-2 vaccines for patients with known autoimmune hepatitis

Patients with chronic liver diseases (CLD), especially those with cirrhosis, have an increased mortality risk when infected by SARS-CoV-2 [1]. One of the largest international studies currently available, showed an observed mortality of 32% in patients with cirrhosis compared to 8% in those without [2]. Therefore, the European Association for the Study of the Liver (EASL) has recommended

vaccination against SARS-CoV-2 for all patients with CLD [3]. Although contrasting data have been published, patients with AIH with or without cirrhosis under immunosuppressive therapy represent an at-risk category of developing severe COVID-19 when infected [4,5]. Therefore, based on the data available, the benefit of anti-SARS-CoV-2 vaccination outweighs the potential risk for disease exacerbation in AIH.

Although the registration trials of mRNA vaccines enrolled patients with CLD (217 patients in Pfizer trial and 196 patients in Moderna trial), subjects under immunosuppressive therapy were excluded. A recent study by Thuluvath and colleagues found that 75% of patients with CLD without cirrhosis and 77% of patients with cirrhosis had adequate antibody response to anti-SARS-CoV2 vaccines [6]. The authors included 233 patients with CLD with 61

* Corresponding author at: Department of Biomedical Sciences, Humanitas University; Division of Internal Medicine and Hepatology, Department of Gastroenterology, IRCCS Humanitas Research Hospital, Via A. Manzoni 56, Rozzano 20089, Italy.

E-mail address: ana.lleo@humanitas.it (A. Lleo).

being affected by immune mediated liver diseases, including AIH, primary biliary cholangitis, and primary sclerosing cholangitis. Also 62 patients were liver transplant (LT) recipients, 79 had cirrhosis, and 92 had CLD without cirrhosis. Antibody levels were undetectable in 11 patients who had LT, 3 with cirrhosis, and 4 without liver cirrhosis. LT and treatment with two or more immunosuppressive drugs were associated with poor antibody responses. However, only 3 patients out of 18 with undetectable antibody were AIH patients on immunosuppression (2 on prednisone plus mycophenolate mofetil (MMF) and 1 on prednisone plus azathioprine).

Reports have shown a reduced antibody response following the full course of vaccination in liver transplant recipients [7]. It has also been formerly demonstrated that specific drugs (*i.e.* methotrexate, abatacept, and rituximab) reduced the immune response to influenza or pneumococcal vaccines in a number of different rheumatic diseases [8–10]. The efficacy of anti-SARS-CoV-2 vaccination in preventing COVID-19 in patients with AIH on immunosuppressive therapies [11,12], as well as the risk of disease reactivation after anti-SARS-CoV-2 vaccination, have been poorly investigated. Similarly, cellular immunity to SARS-CoV-2 in AIH patients has not been studied.

The American College of Rheumatology (ACR) has recently proposed a guidance [13] suggesting a short-term withdrawal of methotrexate, JAK inhibitors, abatacept, and MMF, and deferral of rituximab and cyclophosphamide infusion if possible before anti SARS-Cov-2 vaccination, according to rheumatic disease activity. However, there is no solid evidence as to whether it is appropriate or not to suspend or reduce the dose of immunosuppressive drugs immediately before or following the administration of the vaccine in AIH patients. Importantly, this strategy may be potentially associated with an increased risk of AIH reactivation particularly dangerous in patients with cirrhosis. Of interest, high doses of MMF and rituximab remain independent predictors of failure to develop an antibody response after vaccination in rheumatic diseases [14]; however, no data are available in AIH. At the present time, the available data do not justify withdraw or reduction of immunosuppression before or immediately after vaccination in patients with AIH.

Finally, no clear evidence of reactivation of AIH after anti-SARS-CoV-2 vaccination has been reported in the literature. Interestingly, the presence of significant fibrosis at the liver histology of a small number of newly diagnosed AIH following anti-SARS-CoV-2 vaccination might suggest the possibility of disease reactivation [15–17]. However, until new multicenter studies are available there is no current indication for routine testing of transaminases levels in AIH patients after vaccination.

2. 2022 aisf recommendation on autoimmune hepatitis like onset following anti-SARS-CoV-2 vaccination

The COVID-19 pandemic has necessitated the development and registration of several vaccines in record time. The monitoring for safety, side effect and efficacy is ongoing in the post-marketing surveillance. Recent reports inform on the possible occurrence of immune mediated hepatitis or AIH-like disease in predisposed individuals. Autoimmunity is widely accepted to develop in genetically predisposed individuals and some polymorphisms have been identified in AIH [18]; unfortunately, they are not yet of clinical use and cannot be of help to identify individuals at risk.

Considering that 58% of the world population has received at least one dose of anti-SARS-CoV-2 vaccine, with 9.2 billion doses been administered globally, it is unclear whether this is a pure co-incidence rather than a causality.

The fact that someone developed immune-mediated acute hepatitis after vaccination does not necessarily mean that this was caused by the vaccine.

The European Medicine Agency (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC) has recently started an assessment following the very small number of cases reported after vaccination with Spikevax® and Comirnaty® (known as Moderna and Pfizer vaccines, respectively) in the medical literature and EudraVigilance (www.ema.europa.eu). Further data and analyses have been requested from the marketing authorization holder to support the ongoing assessment by PRAC. Given the small number of cases currently reported, the issue seems to be rare; however, specific studies should be performed to define the number and severity of cases.

At the time these recommendations are drafted, 17 reports have been published in the medical literature that overall include 31 cases of suspected AIH-like triggered by the vaccine (Table 1). Patients were more often women (F:M 21:10), age ranging from 32 to 89 years old (median 58 years). In eleven cases a pre-existent autoimmune condition (*i.e.*, seven Hashimoto thyroiditis, one primary biliary cholangitis, two rheumatoid arthritis, one systemic lupus erythematosus) is reported. Two patients had experienced COVID-19 infection before the vaccine. All except four presented with an acute onset of AIH-like with jaundice. All patients underwent liver biopsy and in six of them fibrosis was already present, which might suggest that they had a previous liver disease, possibly an undiagnosed AIH. All were treated with steroid therapy, and all improved the liver function tests (LFTs), although details on the biochemical response are not thoroughly reported.

Adverse effects of the vaccine are possible, and abnormal liver function tests following vaccination represent an important clinical issue. AIH is a relatively rare, chronic immune-mediated liver disease, which develops in genetically predisposed individuals following environmental triggers; viral infections and drug exposures have been suggested to trigger the disease, but not definitive evidence is available [19,20]. AIH-like onset after vaccination - other than anti-SARS-CoV-2 - has been also previously reported [21]. However, even if it can be speculated that the vaccines can disturb self-tolerance and trigger autoimmune responses through cross-reactivity with host cells, it might be hard to definitively state that AIH is induced by a vaccine. Considering the reported AIH-like cases following SARS-CoV-2 vaccination, timing of occurrence of acute hepatitis from vaccination in some of them is very short (less than 7 days), suggesting that a dysregulation of immune system has already occurred before vaccination in those cases. So far, given the availability of only observational literature without a structured collection of AIH-like cases after anti-SARS-CoV-2 vaccines, no definitive conclusions can be drawn. There is a need for population-based studies to gather data on the incidence, severity, and clinical features of anti-SARS-Cov-2 vaccination-induced AIH under the umbrella of the national and European Scientific Societies.

In the meantime, while intensive vaccination against SARS-CoV-2 continues, healthcare providers should include the diagnosis of AIH triggered by vaccines in the differential diagnosis in cases of acute hepatitis of unexplained etiology and manage them as drug-induced AIH or AIH-like liver injury as recommended by current guidelines [22].

3. RECOMMENDATIONS

**These recommendations will be reviewed periodically as further information becomes available.*

- **AIH patients should receive anti-SARS-CoV-2 vaccination** consistent with the age restriction of the local approval. In Italy, as

Table 1
Cases of suspected AIH triggered by the vaccine reported in the literature.

Reference	Vaccine	Patient's characteristics				Clinical presentation and laboratory data	Therapy	Outcome
		Age, gender	Autoimmune comorbidities	Previous COVID-19 infection	Other comorbidities			
Avci & Abasiyanik [15]	mRNA Pfizer/BioNTech, 1 month before	61, F	Hashimoto thyroiditis	Yes, mild, 8 months before	Hypertension	Acute icteric ANA, ASMA, hyper-IgG, fibrosis F2,	Prednisolone + azathioprine add-on	35 days follow-up, mild transaminases and bilirubin
Bril et al. [16]	mRNA Pfizer/BioNTech, 7 days before	35, F	Not reported	No	Gestational hypertension and cesarian section 3 months before	Acute icteric, normal IgG, no fibrosis	Prednisone 20 mg/day	50 days follow-up, transaminases normalization
Cao et al. [17]	Inactivated whole-virion SARS-CoV2 (Coronavac)	57, F	Not reported	No	Not reported	Acute icteric, pruritus IgG slight elevation, ANA+, Fibrosis F2	Methylprednisolone, UDCA + azathioprine add-on	5 months follow-up, no relapse
Clayton-Chubb et al. [23]	ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca), 26 days before	36, M	No	No	Hypertension, laser eye surgery 2 weeks before	Acute, sub-icteric, asymptomatic, ANA+, normal IgG, no fibrosis	Prednisolone 60 mg/day	24 days, normalization of bilirubin, marked reduction of ALT
Garrido et al. [24]	mRNA Moderna, 2 weeks before	65, F	No	No	Polycythemia vera under PEG-IFN	Acute icteric severe, ANA, hyper-IgG, no fibrosis	Prednisolone 60 mg/day	1 month, improvement of LFTs and IgG normalization
Ghielmetti et al. [25]	mRNA-1273, 7 days before	63, M	No	No, unknown but anti-cardiolipin+	Type 2 diabetes, ischemic heart disease	Acute icteric, hyper-IgG, ANA+, AMA+ (different from PBC) APCA+, no fibrosis	Prednisone 40 mg/day, rapidly tapered	14 days follow-up
Goulas et al. [26]	mRNA Moderna, 2 weeks before	52, F	No	No		Acute icteric, ANA+, ASMA+, hyper-IgG, no fibrosis reported	Prednisolone 50 mg/day, azathioprine add-on	Unknown
Londono et al. [27]	mRNA Moderna, 7 days after the II dose	41, F	Not reported	No	Hormonal therapy for premature ovarian failure	Acute icteric, ANA, ASMA, anti-SLA/LC+, hyper-IgG, no fibrosis	Prednisone 1 mg/Kg	Normalization of LFTs
Palla et al. [28]	mRNA Pfizer/BioNTech 1 month after II dose	40, F			Sarcoidosis	Transaminases 3–4 x ULN fluctuation, ANA+, hyper-IgG, active hepatitis, fibrosis with septa	Prednisolone 40 mg/day	Transaminases decline after 7 days of prednisolone
Rela et al. [29]	ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca), 20 days before	38, F	No (hypothyroidism?)	No	Hypothyroidism	Acute icteric, ANA+, IgG mildly elevated, multiacinar hepatic necrosis, no fibrosis	Prednisolone 30 mg/day and tapering after 4 weeks	1 month of follow-up normal LFTs
	ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca), 16 days before	62, M			2 episodes of jaundice resolved with native medication	Acute severe AIH, autoantibodies negative, mild fibrosis	Prednisolone 30 mg/day + plasma exchange 5 cycles	Persistent cholestasis → death in 21 days for economic constraints regarding liver transplantation
Rocco et al. [30]	Pfizer/BioNTech 1 week before (II dose)	89, F	Hashimoto thyroiditis	No	Previous acute glomerulonephritis, pravastatin and low-dose aspirin for primary prevention	Acute icteric, ANA+, hyper-IgG, no fibrosis	Prednisone 1 mg/Kg/day and tapering	3 months of follow-up, progressive improvement

(continued on next page)

Table 1 (continued)

Reference	Vaccine	Patient's characteristics				Clinical presentation and laboratory data	Therapy	Outcome
		Age, gender	Autoimmune comorbidities	Previous COVID-19 infection	Other comorbidities			
Tan et al. [31]	mRNA Moderna, 6 weeks before	56, F	Not reported	No	Rosuvastatin	Acute icteric, ANA+, ASMA+, hyper-IgG, also eosinophil, early fibrosis	Budesonide	1 week of follow-up
Tun et al. [32]	mRNA Moderna, 3 days before (I dose) and 2 days before (II dose)	47, M	Not reported	No	Not reported	Acute icteric, ANA+ hyper-IgG, rapidly resolved and then reappeared 2 days after the II dose, minimal fibrosis	Prednisolone 40 mg/day	2 weeks of follow-up PT normalized
Vuille-Lessard et al. [33]	mRNA Moderna, 3 days before	76, F	Hashimoto thyroiditis	Yes, 3 months before (mild disease)	Prior urothelial carcinoma	Acute icteric, hyper-IgG, ANA+, ASMA+, ANCA+, steatosis, active AIH, fibrosis not evaluable	Prednisolone 40 mg/day + azathioprine add-on 2 weeks after	4 months follow-up: LFTs normalization after 4 weeks, stop azathioprine and 6 weeks after no relapse
Suzuki Y et al. [34]	mRNA Pfizer/BioNTech 10 days before (II dose)	80, F	Not reported	Not reported	Gastroesophageal reflux esophagitis	Acute icteric, ANA+, hyper-IgG	Prednisone at an initial dose of 0.8 mg/kg/day, then tapered to 10 mg/week	50 days of follow-up: transaminases normalization
	mRNA Pfizer/BioNTech 4 days before (II dose)	75, F	Not reported	Not reported	Dyslipidemia	Acute icteric, ANA+, AMA+, hyper-IgG	Prednisone at an initial dose of 1 mg/kg/day, then tapered to 10 mg/week	105 days of follow-up: transaminases normalization
	mRNA Pfizer/BioNTech 7 days before (I dose)	78, F	Primary biliary cholangitis	Not reported	No	Acute, ANA+, AMA+, hyper IgG	Prednisone at an initial dose of 0.6 mg/kg/day, then tapered to 10 mg/week	103 days of follow-up: transaminases normalization
Torrente et al. [35]	ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca), 3 weeks before	49, F	Hypothyroidism (?), ANA+	No	Hypothyroidism treated with levothyroxine	Acute AIH, ANA+, hyper-IgG, no fibrosis	Prednisone 30 mg/day then tapering and azathioprine add-on	Transaminases decrease after 2 weeks
Rigamonti C et al. [36]	mRNA Pfizer/BioNTech, 7 patients mRNA Moderna, 2 patients ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca), 3 patients	median age 62 years (range 32–80) 6 F, 6 M	3 thyroiditis, 2 rheumatoid arthritis, 1 systemic lupus erythematosus			10 acute onset, 8 jaundice, 8 positive autoantibodies (6 ANA, 1 SMA, 1 LKM-1)	Prednisone / prednisolone +/- azathioprine	median follow-up 3 months: 58% complete biochemical response
Efe C et al. [37]	mRNA Pfizer/BioNTech, 1 patient	53, M	None	Not reported	None	Acute icteric hepatitis, no ANA, hyper-IgG, no fibrosis	prednisolone (40 mg/day) and plasma exchange	Liver transplantation

recommended by the Italian Ministry of Health for all immunosuppressed patients, mRNA vaccines should be used. Based on the data for the mRNA vaccines available, there is no preference for one vaccine over another.

- Patients with **AIH** are suggested to undergo vaccination when the disease activity is controlled by immunosuppressive therapy. To date there are no data available to establish variations on the interval between doses of anti-SARS-CoV2 vaccine.
- There is **no current evidence to recommend suspension or reduction** of immunosuppressive drugs in AIH patients before or immediately after anti-SARS-CoV-2 vaccination.
- The risk of AIH flare or disease worsening following anti-SARS-CoV-2 vaccination has not been assessed to date and specific studies are required before defining a line of recommendation. Based on available data **routine testing of transaminases** levels in AIH patients after vaccination could be suggested in selected patients although the timing needs to be defined.
- **Testing of antibody** levels for IgM and/or IgG to spike or nucleocapsid proteins to assess immunity to SARS-CoV2 after vaccination in AIH patients is not recommended, nor to assess the need for vaccination in an unvaccinated AIH patients.
- Patients with new **acute onset of liver injury following anti-SARS-CoV-2 vaccine** should be managed as suggested by current guidelines and known clinical algorithms, including the indication to liver biopsy. Considering the lack of evidence currently available to exclude drug induced AIH in this setting, immunosuppressive therapy should be carefully considered and used if AIH diagnosis is confirmed; long-term immunosuppressive therapy needs to be assessed on a patient-by-patient basis.
- Patients with **newly diagnosed AIH or AIH flare after anti-SARS-CoV-2 vaccine** should be consider for vaccine booster; however, the timing of the booster could be personalised based on the disease activity and ongoing therapy and discussed case-by-case with an expert center in autoimmune liver diseases.
- Given the limited number of cases compared to the number of vaccinated subjects, extended **testing of transaminases level after vaccination** in the general population is not sustainable nor suggested.
- EMA's PRAC encourages all healthcare professionals and patients to **report any cases** of autoimmune hepatitis and other adverse events in people after vaccination.

Declaration of Competing Interest

None declared.

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