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Francesca Lodato^{1,*}

Anna Larocca¹

Antonietta D'Errico²

Vincenzo Cennamo¹

¹Gastroenterology and Interventional Endoscopy Unit, Azienda Unità Sanitaria Locale di Bologna Bellaria-Maggiore Hospital, Bologna, Italy

²Pathology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy

*Corresponding author. Address: Unit of Gastroenterology and Interventional Endoscopy, AUSL Bologna Bellaria-Maggiore Hospital, Largo Bartolo Nigrisoli 2, 40100, Bologna, Italy. Tel./fax: +390516478536.

E-mail address: francesca.lodato@ausl.bo.it (F. Lodato)



Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: One or even several swallows do not make a summer

To the Editor:

I read with interest the comments to our letter by Londoño *et al.*,¹ Clayton-Chubb *et al.*,² Tan *et al.*,³ McShane *et al.*,⁴ and Lodato *et al.*,⁵ and I appreciate their contribution. All these authors presented similar cases of autoimmune hepatitis (AIH) that developed after coronavirus disease 2019 (COVID-19) vaccine, with the exception of Lodato *et al.*,⁵ who actually described a case of acute liver injury with some features of autoimmunity.

First of all, I was glad to see the repercussions of our manuscript, as it triggered the publication of many similar cases. Only by sharing experiences we will be able to learn more about COVID-19 infection and the effects of its vaccines. Our observation was evidently not an isolated finding, and similar presentations were observed worldwide.

Capecchi *et al.*⁶ suggested that a period of time of 6 days after vaccine administration, as seen in our case,⁷ seemed inconsistent with an immunopathologic reaction. However, among these 5 other cases, the latency period was similarly short and ranged from only 4 to 35 days. With some small variations, the cases also shared similar biochemical, immunological, and histological characteristics (Table 1). Indeed, a peculiarity

among all these cases was a histology with characteristics of an immune process with features of drug-induced toxicity. Moreover, the rate and speed of improvement with glucocorticoids appeared to be similar in all the cases, and no relapses have been observed thus far. Only a longer follow-up will help us assess the risk of relapses in these cases. Further supporting a link between the vaccines and AIH, some of the authors even observed worsening of the symptoms after the second dose of the vaccine.^{1,5}

However, while the resemblance of all these cases suggests a potential causal link between the vaccine and AIH, as the title of this article suggests, this cannot be taken as proof that this link really exists. Considering an annual incidence of 1 case per 100,000 inhabitants as previously reported,⁸ and assuming an even distribution during the 12 months, we can estimate 1 monthly case per 1,200,000 inhabitants. Based on CDC data, during the first month of the US COVID-19 vaccination program, approximately 13,000,000 people received at least 1 dose of the vaccine (available at <https://covid.cdc.gov/covid-data-tracker/#vaccinations>). Based on AIH incidence, we can therefore roughly estimate that ~10 people from this vaccinated cohort would have developed AIH within a month of getting the vaccine. Thus, it should not be surprising that we will all continue to see these cases as we continue with our vaccination efforts. Epidemiological studies assessing changes in AIH incidence may

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Table 1. Characteristics of patients with autoimmune hepatitis after COVID-19 vaccination.

Study	Patient's characteristics	Vaccine	Latency period (days)	AST/ALT at presentation (U/L)	Bilirubin at presentation (mg/dl)	Ab	IgG	Biopsy consistent with AIH
Bril <i>et al.</i>	Female, 35	Pfizer (1 st dose)	13	754/2,001	4.8	ANA ds-DNA	N	Yes
Londoño <i>et al.</i>	Female, 41	Moderna (2 nd dose)	7	993/1,312	2.3	ANA SMA SLA LC1	↑	Yes
Clayton-Chubb <i>et al.</i>	Male, 36	Oxford-AstraZeneca (1 st dose)	26	633/1,774	1.0	ANA	N	Yes
Tan <i>et al.</i>	Female, 56	Moderna (1 st dose)	35	1,124/1,701	6.0	ANA SMA	↑	Yes
McShane <i>et al.</i>	Female, 71	Moderna (unknown)	4	?/1,067	12.1	SMA	↑	Yes
Lodato <i>et al.</i>	Female, 43	Pfizer (1 st dose)	15	51/52	17.5	-	N	Yes

ALT, alanine aminotransferase; ANA, antinuclear antibodies; AST, aspartate aminotransferase; ds-DNA, double-stranded DNA antibodies; LC1, liver cytosol antibodies; SLA, soluble liver antigen antibodies; SMA, smooth muscle antibodies.

be able to shed some light on this uncertainty. Only if we observe a true increment of AIH incidence after COVID-19 vaccination, can we make the case for a potential relationship. Until then, primary care providers and hepatologists are encouraged to keep their eyes open and maximize adverse event reporting to the appropriate authorities.

In summary, we need to remain vigilant and stay open to the idea that SARS-CoV-2 infection and its vaccines may induce autoimmune processes, including AIH. However, we do not have any solid proof of a causal relationship. And even if there was a relationship, it is probably the result of cross-reactivity to the viral spike protein⁹ and likely to be much worse after COVID-19 infection than vaccination. Writing from Alabama, a US state with one of the lowest vaccination rates, I am witnessing first-hand the consequences of low vaccination rates. Therefore, it is crucial that we continue to promote widespread vaccination. Only with this strategy will we be able to ultimately defeat COVID-19.

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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.

Supplementary data

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Fernando Bril*

Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

*Corresponding author. Address: Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA; Tel.: 205-934-2490.

E-mail address: fbril@uab.edu