COVID-19 vaccination as a trigger of IgA vasculitis: a global pharmacovigilance study

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Key messages:

This study provides safety data on IgAV associated with COVID-19 vaccines.

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Data availability statement

We thank Vigibase for giving us access to the data. The data supplied to Vigibase come from a variety of sources, and the likelihood of a causal relationship is not the same in all reports. The

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The data underlying this article are available in VigiBase at https://www.who-umc.org/vigibase/vigibase/, and can be accessed with a personal identifier, as part of the network of pharmacovigilance centers and the WHO Programme for International Drug Monitoring.

Abstract

Introduction: IgA vasculitis (IgAV) can occur after vaccination. We aimed to assess a potential safety signal on the association between COVID-19 vaccines and IgAV.

Patients and methods: Cases of IgAV involving COVID-19 vaccines were retrieved in Vigibase. Disproportionate reporting was assessed using the Bayesian information component with all other drugs and vaccines as control groups.

Results: Three hundred and thirty de novo IgAV from 24 countries were included, mostly in United States (193/330, 58%). Fifty per cent were female (163/328), median age was 32 years [interquartile range (IQR), 15-59] of which 33% (84/254) were young (1-17 years). Median time to onset of IgAV was 7 days (IQR, 2-16; n=256) and 85% of patients (280/330) were vaccinated with mRNA vaccines. Seriousness was reported in 188 cases (58%). Ninety-five recovered (65%) and 2 died (2%). A positive rechallenge was reported for 3 of 4 patients (75%).

A total of 996 cases of IgAV were identified with other vaccines. There was a small significant increase in IgAV reporting with COVID-19 vaccines compared with all other drugs (IC 0.22, credibility interval (CrI) from 0.04 to 0.35). No disproportionality signal was found between COVID-19 and other vaccines (IC -1.42, CrI from -1.60 to -1.28]). There was no significant difference between mRNA vaccines and viral vector COVID-19 vaccines. Men and children had a significant overreporting of IgAV compared with women and adults, respectively.

Conclusion: This study, provides reassuring results regarding the safety of COVID-19 vaccines in the occurrence of IgAV compared to other vaccines.

1. Introduction

IgA vasculitis (IgAV) is an immune complex vasculitis (1) affecting mainly small size vessels (2). IgAV can occur after respiratory or digestive mucosa infections but can also be induced by vaccine as influenza, and the diphtheria tetanus pertussis (DTP) vaccine (3–5).

COVID-19 pandemic outbreak triggered a worldwide vaccination campaign, using mainly a new messenger Ribonucleic Acid (mRNA) based technology (6) followed by several reports of related autoimmune manifestations (7,8). Cases of vasculitis, including newly developed or relapsed IgAV have also been reported (8–11). However incidental findings cannot be ruled out. Using Vigibase, the WHO pharmacovigilance database that gathers individual case safety reports (ICSRs) of adverse drug reactions (ADRs) reported trough national pharmacovigilance systems from over 150 countries worldwide since 1968, we aimed to assess a potential safety signal on the association between COVID-19 vaccines and IgAV.

2. Material and methods

Population

In this observational disproportionality study, all ICSRs reported as de novo IgAV cases involving COVID-19 vaccines (elasomeran, tozinameran, ChAdOx1 nCoV-19 and JNJ-Ad26.COV2.S) until June 01, 2022, were retrieved in Vigibase using the previously validated Medical Dictionary for Regulatory Activities (MedDRA) lowest level terms (12). We included all patients corresponding to the MedDRA lowest level terms: “Rheumatic purpura”, “Henoch-Shonlein purpura”, “Henoch-Schonlein”, “Henoch-Schonlein purpura”, “Schoenlein-Henoch purpura”, “Vasculitis Henoch-Schonlein like”, “IgA vasculitis” and “IgA-associated vasculitis”. De novo IgAV cases were identified by excluding cases with an underlying worsening of IgAV co-reported using the MedDRA Preferred Terms "Condition aggravated" and "Concomitant disease aggravated".

For each ICSR, extracted data included administrative information (date, country, reporter qualification), patient demographics (age, sex), exposure characteristics (drug name,

rechallenge) and IgAV features [time to onset, seriousness, outcome, positive rechallenge (i.e., recurrence of IgAV after an additional COVID-19 vaccines]. The time to onset was computed as the time (in days) between the last available shot date and the date of the IgAV onset.

Per the Jardé law in France regarding research involving human participants, no ethical review or informed consent was required because an existing anonymized database was used.

Statistical analysis

Disproportionate reporting was assessed using the Bayesian information component (IC) which displays the best sensitivity and specificity among disproportionality methods (13), with all other drugs and all other vaccines (ATC J07A-X) as control groups. Only drugs characterized as suspect or interacting according to the WHO, ie the drugs that had the most likely causal relationship with the ADR, definition were considered. Pharmacovigilance disproportionality analyses is considered a relevant tool for identifying new drug-ADR-associated potential safety signals, using spontaneous reports as material (14). The concept of disproportionality is based on the comparison of the reporting proportions between the study drug (e.g., COVID-19 vaccines) and the comparator (e.g., all other drugs, all other vaccines) in a spontaneous reporting database. In other words, this study design is intended to highlight the existence or absence of an increase (disproportionality) in the number of observed cases as compared to the expected number of cases where the overall reporting rate of the ADR of interest for the comparator is used as a proxy for the background occurrence of the ADR (15). Table 1 describes the contingency table of the disproportionality study and the formulas for estimating the IC and its 95% credibility interval (CrI). A signal of disproportionate reporting of IgAV was defined as an IC with a 95% CrI lower boundary that exceeded 0 (16).

Several sensitivity analyses were performed, including 1) restriction to IgAV cases with the solely drug with the higher imputability score to calculate the IC, 2) restriction to IgAV that occurred within 30 days after vaccine administration to increase the likelihood that signals were true adverse drug reactions, and 3) exclusion of vaccine-associated ICSRs with reactogenicity events (MedDRA Preferred Terms 'Headache' and 'Pyrexia') to limit the risk of a competition bias between events that may mask a true safety signal (17).

The statistical analysis was performed with R, version 4.1.3 (R Foundation).

3. Results

Of the 31,738,658 ICSRs in Vigibase until June 01, 2022, 3,712,164 were related to COVID-19 vaccines including 330 *de novo* IgAV from 24 countries, of which the three largest contributors were the United States (193/330, 58%), the United Kingdom (31/220, 9%) and France (29/330, 9%). Among these patients 50% were female (163/328), the median age was 32 years [interquartile range (IQR), 15-59] of which 17% (42/254) were child (1-12 years), 17% (42/254) were adolescent (12-17 years), 48% (122/254) were adult (18-65 years) and 19% (48/254) were elderly (>65 years). The median time from vaccination to onset of IgAV was 7 days (IQR, 2-16; n=256) and 85% of patients (280/330) were vaccinated with mRNA vaccines. Seriousness as defined by the WHO criteria (12) was reported in 188 cases (58%). Of the 147 cases where disease outcome was available at the time of reporting, 95 recovered (65%) of which one with sequelae, and 2 died (2%). A positive rechallenge was reported for 3 of 4 patients (75%) who received a new dose of COVID-19 vaccine.

A total of 2,093 cases of IgAV were identified with other drugs than COVID-19 vaccines, including 996 with other vaccines (Figure 1). There was a small significant increase in IgAV

reporting with COVID-19 vaccines compared with all other drugs (IC 0.22, CrI from 0.04 to 0.35). No disproportionality signal was found when COVID vaccines were compared with other vaccines (IC -1.42, CrI from -1.60 to -1.28]). The results were consistent in all sensitivity analyses where no significant overreporting of IgAV was found compared with other vaccines (Figure 1).

In our subgroup analyses, no significant difference was found in IgAV reporting between mRNA vaccines and with viral vector vaccines COVID-19 even after stratification on age. Among patients exposed to COVID-19 vaccines, men and children had a significant overreporting of IgAV compared with women and adults, respectively (Figure 1).

4. Discussion

Altogether our results showed that COVID-19 vaccines are associated with a slight but significant overreporting of IgAV but not greater than that observed with other vaccines. Of note, both sex ratio and mean age of IgAV following COVID-19 were roughly comparable to those induced by viral conditions or drugs (18,19). Despite the small number of cases considered, the existence of positive rechallenge with IgAV relapse in this study, and the demographic characteristics of the reported cases support the hypothesis of a triggering effect of COVID-19 vaccines. To explain this possible effect one of our hypothesis is, a vasculitis driven hypoglycosylated IgA- mediated response following vaccination. Indeed, an IgA response have been observed after BnT162B2 and ChAdOx1 vaccination(20,21). Moreover, IgA are known to play a pivotal role during the onset of IgAV forming immune complexes, which further activate the immune system (22).

We also confirmed the results of a recent study that compared the reporting of systemic vasculitis (including relapses) associated with COVID-19 mRNA vaccines versus influenza vaccines (23), extending it to others vaccines. Our results should be viewed in light of the known limitations of the spontaneous reported cases. First, under-reporting is frequent and, therefore, the selective nature of spontaneous reporting may result in lack of representativeness. Second, some important data were missing (e.g., outcomes) and cases do not contain sufficient clinical data to ascertain the IgAV diagnosis by external review with the use of this database. This may have impacted the results of the disproportionality analysis under the assumption of differential reporting quality between COVID-19 vaccines and the other drugs used as comparators. Nevertheless, to increase the likelihood that the potential signals were true adverse drug reactions, we included in sensitivity analyses only patients who developed IgAV within 30 days of COVID-19 vaccination and only ICSRs where vaccines were sole suspected drugs in the occurrence of IgAV, with consistent results. Further studies are needed both to confirm or refute these results on the association between COVID-19 vaccination and IgAV using other data sources. Then comparing a cohort of IgAV induced by COVID-19 vaccines to IgAV without any previous vaccination could have been interesting but precise clinical data of IgAV following COVID-19 are lacking to perform such comparison.

5. Conclusion

COVID-19 vaccines, like other vaccines, could serve as a trigger for the expression of a first episode of IgAV in predisposed patients. This study, however, provides reassuring results regarding the safety of COVID-19 vaccines in the occurrence of IgAV compared to other vaccines.

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Table | Contingency table for the case-non-case analysis and operative definitions of the information component used as measure of disproportionality.

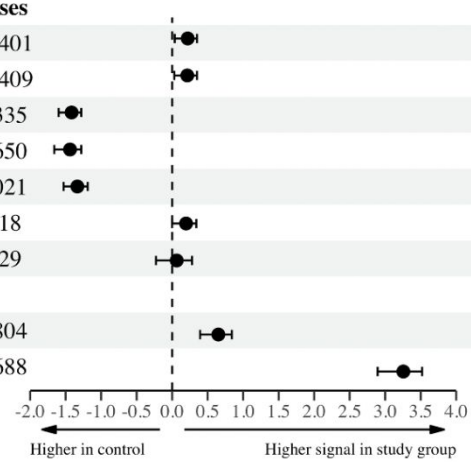
	Reported IgAV (cases)	Other reported ADRs without IgAV (non-cases)
Study group: drugs of interest (e.g., COVID-19 vaccines)	*a*	*b*
Control group (e.g., all other drugs)	*c*	*d*

Estimator	Estimator formula	Credibility interval formula	Condition for SDR
IC (16)	$IC = \log2\left(\frac{Nobserved + 0.5}{Nexpected + 0.5}\right) = \log2\frac{a + 0.5}{\frac{(a+b)*(a+c)}{a+b+c+d} + 0.5}$	$IC_{LB} = IC - 3.3\cdot(a+0.5)^{-1/2} - 2\cdot(a+0.5)^{-3/2}$ $IC_{UB} = IC + 2.4\cdot(a+0.5)^{-1/2} - 0.5\cdot(a+0.5)^{-3/2}$	$IC_{LB} > 0$

IC, information component; IC_{LB}, lower boundary of the 95% credibility interval; IC_{UB}, upper boundary of the 95% credibility interval; IgAV, immunoglobulin A vasculitis; SDR, signal of disproportionate reporting

Figure 1 | Forest plot of the information component values of COVID-19 vaccine–associated de novo IgA vasculitis vs all other drugs and all other vaccines and subgroup analyses by vaccine type, age and sex.

	Study group		Control group		
Comparison (study vs control groups)	**IgAV cases**	**Non cases**	**IgAV cases**	**Non cases**	**IC [CrI 95%]**
COVID-19 vaccines vs all other drugs	330	3711834	2093	28024401	0.2 (0.0 to 0.3)
COVID-19 vaccines vs all other drugs, single suspect	327	3711837	2085	28024409	0.2 (0.0 to 0.3)
COVID-19 vaccines vs other vaccines	330	3711834	996	1871335	-1.4 (-1.6 to -1.3)
COVID-19 vaccines vs other vaccines, TTO ≤30 days	221	3711943	681	1871650	-1.4 (-1.7 to -1.3)
COVID-19 vaccines vs other vaccines, excl. of reactogenicity events	291	2489394	850	1376021	-1.3 (-1.5 to -1.2)
mRNA vaccines vs viral vector COVID-19 vaccines	280	2756380	50	966718	0.2 (-0.0 to 0.3)
mRNA vaccines vs viral vector COVID-19 vaccines (adult patients)	128	2230476	42	866729	0.1 (-0.2 to 0.3)
Male vs female (COVID-19 vaccines)	165	1172681	163	2494804	0.7 (0.4 to 0.8)
Children vs adults (COVID-19 vaccines)	84	104817	170	3086688	3.3 (2.9 to 3.5)



COVID-19 vaccines were mRNA vaccines (elasomeran, tozinameran) or viral vector vaccines (ChAdOx1 nCoV-19 and JNJ - Ad26.COV2.S)

The definition of IgAV corresponds to the following Medical Dictionary for Regulatory Activities (MedDRA) lowest level terms: “Rheumatic purpura”, “Henoch-Shonlein purpura”, “Henoch-Schonlein”, “Henoch-Schonlein purpura”, “Schoenlein-Henoch purpura”, “Vasculitis Henoch-Schonlein like”, “IgA vasculitis” and “IgA-associated vasculitis”. De novo IgAV cases were identified by excluding cases with an underlying worsening of IgAV co-reported using the MedDRA Preferred Terms: "Condition aggravated" and "Concomitant disease aggravated".

The excluded reactogenicity events correspond to the two most reported for COVID-19 vaccines: "Headache" and "Pyrexia" (MedDRA Preferred Terms).

IgAV, immunoglobulin A vasculitis; IC, information component; CrI, 95% credibility interval; TTO, time to onset; MedDRA, Medical Dictionary for Drug Regulatory Activities