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# Letter to the Editor (Other)

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## Risk of systemic vasculitis following mRNA COVID-19 vaccination: a pharmacovigilance study

**Rheumatology key message**

- Compared with influenza vaccines, systemic vasculitis reporting is not increased with mRNA COVID-19 vaccines, except eventually for Behçet's syndrome.

Dear Editor, Sporadic cases of systemic vasculitis following coronavirus disease 2019 (COVID-19) vaccination were anecdotally reported in the literature [1, 2], raising the question of the association between vasculitis onset and vaccination during the COVID-19 pandemic. We recently showed that GCA and PMR may be associated with COVID-19 vaccines, although risk of reporting these entities appears lower than with influenza vaccines [3]. Here we aimed to assess a potential safety signal for the different types of systemic vasculitis following mRNA COVID-19 vaccination.

We used VigiBase (https://www.who-umc.org/vigibase/vigibase/), the World Health Organization (WHO) global individual case safety report database that contains spontaneous reports of suspected adverse drug reactions collected by national drug authorities in >130 countries. This large database is powerful for signal detection based on disproportionality analyses [4, 5]. This pharmacovigilance statistical approach is similar to a case–control study nested in a large cohort [4] and estimates whether an adverse event is differentially reported for a specific drug compared with other drugs. The association between an specific adverse event (i.e. a type of vasculitis) and a specific drug (i.e. mRNA COVID-19 vaccines) was expressed using the reporting odds ratio (ROR) and its 95% CI, which corresponds to the exposure odds among reported cases divided by the exposure odds among reported non-cases. To limit indication and reporting bias, comparators were influenza vaccines. A lower boundary 95% CI >1 is deemed significant, as for OR interpretation, and supports a potential safety signal. This study adhered to the Declaration of Helsinki.

Of the 2 499 457 spontaneous reports with mRNA COVID-19 vaccines (i.e. elasomeran/mRNA-1273 and tozinameran/BNT162b2) in VigiBase through 31 March 2022, we identified 2125 (8.5/10 000 reports) vasculitis cases; 61% were women, with median age of 58 years [interquartile range (IQR) 38–72].

Overall, mRNA COVID-19 vaccines were associated with increased reporting in Behçet's syndrome [ROR 1.7 (95% CI 1.4, 2.1)], GCA [ROR 4.5 (95% CI 4.0, 5.0)], microscopic polyangiitis [ROR 2.6 (95% CI 1.8, 3.7)], livedoid vasculopathy [ROR 4.1 (95% CI 2.5, 6.5)] and urticarial vasculitis [ROR 3.0 (95% CI 2.4, 3.7)] (Table 1). None of the other vasculitis types were associated with increased reporting following mRNA COVID-19 vaccines, especially eosinophilic granulomatosis with polyangiitis, Henoch-Schönlein purpura (i.e. IgA vasculitis) or polyarteritis nodosa. When compared with the use of influenza vaccines, we found a disproportionate reporting with mRNA COVID-19 vaccines only for Behçet's syndrome [ROR 4.2 (95% CI 1.3, 13.2)], in a similar manner between elasomeran and tozinameran [ROR 1.7 (95% CI 1.0, 2.9)]. Among the 93 Behçet's syndrome cases, 76 (82%) were women, with a median age of 37 years (IQR 30–43). Differences in systemic vasculitis risk may exist between elasomeran and tozinameran but require further study.

Here we used the WHO global safety database to assess potential safety signals for the different types of systemic vasculitis following the use of mRNA COVID-19 vaccines. We found an increased reporting of Behçet's syndrome, microscopic polyangiitis, livedoid vasculopathy and urticarial vasculitis and, as previously reported, GCA following mRNA COVID-19 vaccination. These findings suggest a potential safety signal for these entities. It should be noted that we previously showed the relative risk for GCA or PMR reporting was reduced with COVID-19 vaccines when the comparator was influenza vaccines [3]. Here, for all vasculitis types except Behçet's syndrome, we did not find increased reporting when compared with influenza vaccines. Behçet's syndrome cases were in the range of the expected epidemiology of this disease. Although significant, these results should be interpreted with caution considering the small number of cases in the comparator group. Environmental factors and infections are likely to play a role in the onset of systemic vasculitis and vaccination could act as an inflammatory trigger, as already suspected in previous studies [6]. Our analysis has limitations such as a underreporting and heterogeneous causality assessment among reports. Also, it highlights the importance of using a relevant comparator for the interpretation of these real-life data.

Overall, our study did not suggest a specific vasculitis risk with mRNA COVID-19 vaccines compared with influenza vaccines, except eventually for Behçet's syndrome. Further analyses are needed to confirm this safety signal and vaccine causality. Nevertheless, mRNA COVID-19 vaccine benefits dramatically

**Table 1** Systemic vasculitis cases reported in the WHO global safety database with mRNA COVID-19 vaccines and their reporting ORs

| Types of vasculitis | $N_{observed}$[a] | | | $N_{expected}$ | $N_{reaction}$ | Disproportionality analysis, ROR (95% CI) | | |
|---|---|---|---|---|---|---|---|---|
| | mRNA COVID-19 vaccines | Elasomeran | Tozinameran | | | mRNA COVID-19 vaccines *vs* any drugs | mRNA COVID-19 vaccines *vs* influenza vaccines | Tozinameran *vs* elasomeran |
| ANCA-associated vasculitis | 229 | 41 | 188 | 255 | 3064 | 0.9 (0.8, 1.0) | 0.4 (0.3, 0.4) | **1.8 (1.3, 2.5)** |
| ANCA-positive vasculitis | 68 | 14 | 54 | 75 | 905 | 0.9 (0.7, 1.1) | 0.3 (0.2, 0.5) | 1.5 (0.8, 2.7) |
| Eosinophilic granulomatosis with polyangiitis | 54 | 11 | 43 | 106 | 1274 | 0.5 (0.4, 0.6) | 0.4 (0.2, 0.7) | 1.5 (0.8, 2.9) |
| Granulomatosis with polyangiitis | 82 | 16 | 66 | 64 | 770 | 1.3 (1.0, 1.7) | 0.3 (0.2, 0.4) | 1.6 (0.9, 2.7) |
| Microscopic polyangiitis | 34 | 3 | 31 | 15 | 180 | **2.6 (1.8, 3.7)** | 0.5 (0.2, 0.9) | **4.0 (1.2, 13.0)** |
| Behçet's syndrome | 93 | 17 | 76 | 57 | 690 | **1.7 (1.4, 2.1)** | **4.2 (1.3, 13.2)** | **1.7 (1.0, 2.9)** |
| Central nervous system vasculitis | 47 | 6 | 41 | 47 | 568 | 1.0 (0.7, 1.3) | 0.6 (0.3, 1.3) | **2.6 (1.1, 6.2)** |
| Cryoglobulinaemic vasculitis | 38 | 1 | 37 | 33 | 401 | 1.2 (0.8, 1.6) | 0.6 (0.3, 1.2) | –[c] |
| Cutaneous vasculitis[b] | 740 | 135 | 605 | 742 | 8921 | 1.0 (0.9, 1.1) | 0.5 (0.4, 0.5) | **1.7 (1.4, 2.1)** |
| Giant cell arteritis | 501 | 99 | 402 | 144 | 1736 | **4.5 (4.0, 5.0)** | 0.7 (0.6, 0.9) | **1.6 (1.3, 1.9)** |
| Henoch, Schönlein purpura | 256 | 51 | 205 | 370 | 4447 | 0.7 (0.6, 0.8) | 0.1 (0.1, 0.1) | **1.5 (1.1, 2.1)** |
| Kawasaki's disease | 45 | 1 | 44 | 118 | 1421 | 0.4 (0.3, 0.5) | 0.1 (0.1, 0.1) | –[c] |
| Liveloid vasculopathy | 24 | 6 | 18 | 7 | 89 | **4.1 (2.5, 6.5)** | –[c] | 1.2 (0.5, 2.9) |
| Polyarteritis nodosa | 24 | 5 | 19 | 64 | 774 | 0.4 (0.2, 0.5) | 0.3 (0.1, 0.5) | 1.5 (0.5, 3.9) |
| Takayasu's arteritis | 9 | 0 | 9 | 17 | 201 | 0.5 (0.3, 1.0) | –[c] | –[c] |
| Urticarial vasculitis and hypocomplementemic urticarial vasculitis syndrome | 93 | 19 | 74 | 37 | 439 | **3.0 (2.4, 3.7)** | 1.1 (0.6, 2.1) | 1.5 (0.9, 2.5) |

The specific types of vasculitis were identified using the ad hoc preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA; https://www.meddra.org/). ROR (95% CI) were calculated as $\frac{ad}{bc}\left(\frac{ad}{bc}.\,e^{\pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}\right)$, where *a* is the number of cases reported with RNA-based COVID-19 vaccines, *b* is the number of non-cases (i.e. all other adverse drug reaction reports) reported with RNA-based COVID-19 vaccines, *c* is the number of cases reported with all other drugs and *d* is the number of non-cases reported with all other drugs. The threshold for signal detection is defined as an ROR lower boundary 95% CI $\geq$1 and the number of cases $\geq$3. Significant associations (adverse event–drug combination) are presented in bold. $N_{expected}$ is the expected number of case reports based on the number of case reports for the drug and for the specific reaction, calculated as $(N_{drug} \times N_{reaction})/N_{total}$, with $N_{total}$ being the total number of reports in the database with any drugs (i.e. 30 031 000 reports) and $N_{drug}$ being the number of reports for the drug, regardless the type of reaction (i.e. 2 499 457 reports with elasomeran or tozinameran); $N_{reaction}$ is the number of reports for the reaction (i.e. cases), regardless of drug. [a]The sum of $N_{observed}$ is greater than the number of cases, as one case may refer to more than one type of vasculitis. [b]Refers to hypersensitivity vasculitis, palpable purpura, vasculitic rash and vasculitic ulcer. [c]ROR not provided because insufficient cases were observed with the studied drugs.

outweigh this potential risk, which appears very rare relative to the billions of doses administered so far.

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## Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

**Camille Mettler[1,2], Benjamin Terrier[2,3], Jean-Marc Treluyer[1,3,*], and Laurent Chouchana[1,*]**

[1]*Assistance Publique-Hôpitaux de Paris, Département de Pharmacologie, Centre Régional de Pharmacovigilance, Hôpital Cochin,* [2]*Assistance Publique-Hôpitaux de Paris, Département de Médecine Interne, Centre de Référence National pour les maladies auto-immunes systémiques rares, Hôpital Cochin and* [3]*Université Paris, Paris, France*
Accepted 25 May 2022
Correspondence to: Laurent Chouchana, Centre Régional de Pharmacovigilance, Hôpital Cochin, 27 Rue du Faubourg Saint-Jacques, 75679 Paris Cedex 14, France.
E-mail: laurent.chouchana@aphp.fr
*L.C. and J.-M.T. are members of the French Pharmacovigilance Network.

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