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ARTICLE

Risk of retinal vein occlusion following COVID-19 vaccination: a self-controlled case series

Marco Pellegrini[1,2,3]✉, Adriano Carnevali[4], Tito Fiore[5], Carlo Cagini[5], Antonella De Palma[5], Luigi Fontana[6], Enrico Lupardi[6], Federico Cassini[6], Daniela Bacherini[7], Fabrizio Giansanti[7], Giuseppe Giannaccare[4], Vincenzo Scorcia[4], Sabrina Vaccaro[4], Nicolò Ciarmatori[1], Sergio D'Angelo[1], Francesco Parmeggiani[1] and Marco Mura[1,8]

BACKGROUND: To evaluate the association between COVID-19 vaccination and retinal vein occlusion (RVO).
METHODS: This multicentre self-controlled case series included patients with RVO seen in five tertiary referral centres in Italy. All adults who received at least one dose of the BNT162b2, ChAdOx1 nCoV-19, mRNA-1273 or Ad26.COV2.S vaccine and had a first diagnosis of RVO between January 01, 2021, and December 31, 2021 were included. Incidence rate ratios (IRRs) of RVO were estimated using Poisson regression, comparing rates of events in a 28-day period following each dose of vaccination and in the unexposed control periods.
RESULTS: 210 patients were included in the study. No increased risk of RVO was observed after the first dose (1–14 days IRR: 0.87, 95% CI: 0.41–1.85; 15–28 days IRR: 1.01, 95% CI: 0.50–2.04; 1–28 days IRR: 0.94, 95% CI: 0.55–1.58) and second dose of vaccination (1–14 days IRR: 1.21, 95% CI: 0.62–2.37; 15–28 days IRR: 1.08, 95% CI: 0.53–2.20; 1–28 days IRR: 1.16, 95% CI: 0.70–1.90). No association between RVO and vaccination was found in subgroup analyses by type of vaccine, gender and age.
CONCLUSIONS: This self-controlled case series found no evidence of an association between RVO and COVID-19 vaccination.

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INTRODUCTION

Despite the success of the coronavirus disease 2019 (COVID-19) vaccination campaign, some concerns have been raised regarding a number of suspected vaccine-related thrombotic events in otherwise healthy individuals who had received either mRNA-based or adenoviral-vectored COVID-19 vaccines [1]. In particular, cases of retinal vein occlusion (RVO) have been reported after the BNT162b2 mRNA (Pfizer-BioNtech) vaccine [2–8], mRNA-1273 (Moderna) vaccine [5, 9] and ChAdOx1 nCoV-19 (AZD1222) vaccine [5, 6, 10].

The current evidence regarding the association, however, is solely based on sporadic case reports. Although a series of anecdotes is not sufficient to prove a causal relationship, it can be enough to bias the public's perception of vaccine safety. This is particularly relevant in view of the emerging evidence supporting a relationship between systemic thrombotic events and vaccination [11]. Since vaccine hesitancy can increase COVID-19-related morbidity and mortality, there is need for stronger evidence on the possible association between COVID-19 vaccination and RVO to provide recommendations for patients, healthcare professionals and policy makers.

The purpose of this study was to determine whether there is evidence of an association between RVO and COVID-19 vaccination.

METHODS

This was a multicentre retrospective self-controlled case series to evaluate the short-term risk of RVO after the first two doses of the BNT162b2, ChAdOx1 nCoV-19, mRNA-1273 and Ad26.COV2.S vaccines. The self-controlled case-series method, which was originally developed to investigate potential associations between vaccines and adverse events [12], determines the incidence of the outcome of interest for exposed time periods (e.g., after vaccination) compared with unexposed control periods. This case-only approach has the advantage of implicitly controlling for all unmeasured time-invariant confounders [13].

Case and vaccine status ascertainment was performed via a retrospective clinical review of hospital records across five tertiary referral centres in Italy (i.e., the S. Anna Hospital, University of Ferrara, the S. Orsola-Malpighi Hospital, University of Bologna, the S. Maria della Misericordia Hospital, University of Perugia, the Careggi University Hospital, University of Florence, and the Mater Domini Hospital, University Magna Graecia of Catanzaro). Patients aged ≥ 18 years who had a first diagnosis of RVO and received first doses of the BNT162b2, ChAdOx1 nCoV-19, mRNA-1273 or Ad26.COV2.S vaccines within the observation period (i.e., the time interval between January 1 and December 31, 2021) were included. Exclusion criteria were: diagnosis of RVO prior to the study period and unavailability of data regarding COVID-19 vaccination status. The diagnosis of RVO was confirmed by ophthalmologists who manually reviewed the retinal images (including fundus photographs, optical coherence tomography, and fluorescein angiography). The diagnosis was based on fundus examination revealing venous dilation and tortuosity, retinal haemorrhages and cotton-

[1]Department of Translational Medicine, University of Ferrara, Ferrara, Italy. [2]Department of Ophthalmology, Ospedali Privati Forlì "Villa Igea", Forlì, Italy. [3]Istituto Internazionale per la Ricerca e Formazione in Oftalmologia (IRFO), Forlì, Italy. [4]Department of Ophthalmology, University Magna Græcia of Catanzaro, Catanzaro, Italy. [5]Department of Biomedical and Surgical Sciences, Section of Ophthalmology, S. Maria della Misericordia Hospital, University of Perugia, Perugia, Italy. [6]Ophthalmology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy. [7]Eye Clinic, Neuromuscular and Sense Organs Department, Careggi University Hospital, Florence, Italy. [8]King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia. ✉email: marco.pellegrini@hotmail.it

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wool spots; and confirmed by fluorescein angiography revealing increased venous transit time, venous filling defects and capillary non-perfusion. In central retinal vein occlusion, retinal haemorrhages were scattered diffusely throughout the four quadrants. In branch retinal vein occlusion, haemorrhages occurred within the localized retinal area corresponding to the blood supply sector of the occluded venule. In hemi-retinal vein occlusion, the involved area comprised either the upper or the lower half of the retina. The study was approved by the local Institutional Review Board and followed the tenets of the Declaration of Helsinki.

The self-controlled case series models were fitted using a conditional Poisson regression to calculate the relative incidence of RVO in the temporal risk periods following vaccination. For each of the first two doses, three risk periods where evaluated: day 1 to day 14, day 15 to day 28 and day 1 to day 28 (day 0 was the day of vaccination) (Fig. 1). The risk periods were established a priori based on published studies reporting RVO occurring within the first four weeks following vaccination [2–10]. A sample size of 167 patients was required to identify a incidence rate ratio (IRR) of 2 using a risk period of 28 days with 80% power. Subgroup analyses were performed by type of vaccine, gender and age (younger or older than 65 years). Sensitivity analyses were conducted by restricting the study period to the time after vaccination (to test the assumption that the occurrence of RVO did not influence the probability of subsequent exposure to vaccination) and censoring on 10 March 2021 (to avoid notoriety bias by excluding the time after which concerns over vaccine-related thrombotic events where first raised). The statistical analysis was performed using the software R (version 4.0.0) and RStudio (version 1.2.5042) with the 'SCCS' package (version 1.5) [14].

RESULTS

In total, 210 patients who were diagnosed with RVO and received the first dose of the BNT162b2, ChAdOx1 nCoV-19, mRNA-1273 or Ad26.COV2.S vaccines between January 1 and December 31, 2021, were included in the study. Table 1 summarizes the demographical and clinical characteristics of included patients. The mean interval between the first and second doses was 44.9 ± 42.4 days. In total, 37 patients (17.6%) received heterologous vaccination with different vaccines in first and second doses.

No increased risk of RVO was observed at 1–14 days (IRR: 0.87, 95% confidence intervals (CI): 0.41–1.85), 15–28 days (IRR: 1.01, 95% CI: 0.50–2.04) and 1–28 days (IRR: 0.94, 95% CI: 0.55–1.58) following the first dose of vaccination. Similarly, no increased risk of RVO was observed after the second dose (1–14 days IRR: 1.21, 95% CI: 0.62–2.37; 15–28 days IRR: 1.08, 95% CI: 0.53–2.20; 1–28 days IRR: 1.16, 95% CI: 0.70–1.90).

Table 2 shows the results of the subgroup and sensitivity analyses. No association between RVO and vaccination was found in males and females, nor in older and younger patients. No increased risk of RVO was found after mRNA and viral vector vaccines, nor after the BNT162b2 and ChAdOx1 nCoV-19 vaccines. The IRRs of RVO after the mRNA-1273 and Ad26.COV2.S vaccines were not calculated due to the low number of cases. In sensitivity analyses performed by restricting the study period to the time

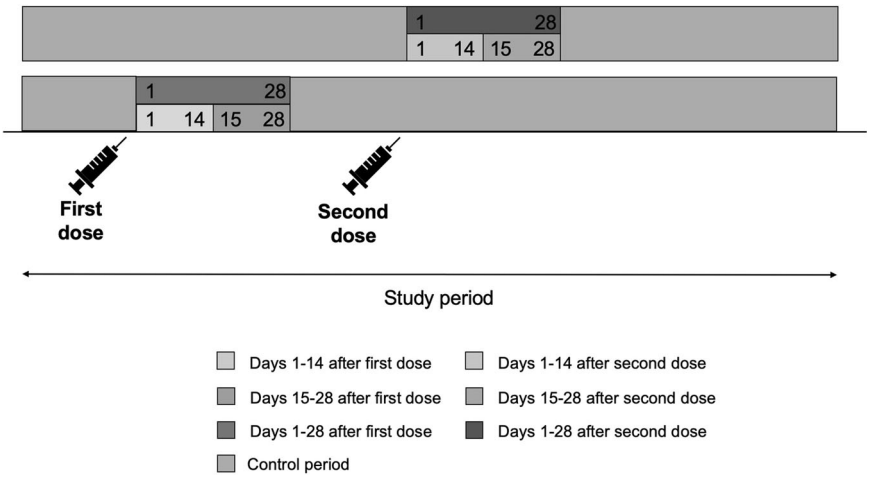

Fig. 1 Schematic representation of the self-controlled case series design. The relative incidence of retinal vein occlusion was derived using a conditional Poisson regression by comparing risk periods of 14 and 28 days after the first dose (green) and second dose (blue) relative to all other observed time (grey).

Table 1. Baseline characteristics of the individuals who underwent COVID-19 vaccination and had a first diagnosis of retinal vein occlusions at the study hospital centres between January and December 2021, stratified by vaccine status.

Variable	Total ($n = 210$)	BNT162b2 ($n = 154$)	ChAdOx1 nCoV-19 ($n = 29$)	mRNA-1273 ($n = 22$)	Ad26.COV2.S ($n = 5$)
Gender, *n* (%)					
Male	111 (52.9)	79 (51.3)	15 (51.7)	15 (68.2)	2 (40.0)
Female	99 (47.1)	75 (48.7)	14 (48.3)	7 (31.8)	3 (60.0)
Age, mean (SD), y	68.8 (12.3)	69.1 (12.1)	70.9 (12.3)	64.5 (14.5)	66.8 (4.3)
Age, *n* (%)					
<65 years	76 (36.2)	58 (37.7)	7 (24.1)	10 (45.5)	1 (20.0)
≥65 years	134 (63.8)	96 (62.3)	22 (75.9)	12 (54.5)	4 (80.0)
Type of occlusion, *n* (%)					
BRVO	99 (47.1)	70 (45.5)	16 (55.2)	10 (45.5)	3 (60.0)
CRVO	91 (43.3)	70 (45.5)	8 (27.6)	11 (50.0)	2 (40.0)
HRVO	20 (9.5)	14 (9.1)	5 (17.2)	1 (4.5)	0 (0.0)

SD standard deviation, *BRVO* branch retinal vein occlusion, *CRVO* central retinal vein occlusion, *HRVO* hemi-retinal vein occlusion.

Table 2. Incidence rate ratio of retinal vein occlusion events at 1–14, 15–28 and 1–28 days after the first and second doses of COVID-19 vaccination by gender, age, type of vaccine, calendar time and restricting the study period to the time after vaccination.

Analysis type	First dose			Second dose		
	1–14 days IRR (95% CI)	15–28 days IRR (95% CI)	1–28 days IRR (95% CI)	1–14 days IRR (95% CI)	15–28 days IRR (95% CI)	1–28 days IRR (95% CI)
Main analysis	0.87 (0.41–1.85)	1.01 (0.50–2.04)	0.94 (0.55–1.58)	1.21 (0.62–2.37)	1.08 (0.53–2.20)	1.16 (0.70–1.90)
Gender						
Male	0.47 (0.12–1.89)	0.96 (0.35–2.59)	0.70 (0.31–1.59)	1.54 (0.67–3.50)	1.01 (0.37–2.74)	1.29 (0.67–2.47)
Female	1.33 (0.54–3.28)	1.06 (0.39–2.90)	1.21 (0.61–2.40)	0.86 (0.27–2.70)	1.17 (0.43–3.18)	1.01 (0.47–2.18)
Age						
<65 years	0.33 (0.05–2.40)	1.03 (0.32–3.27)	0.67 (0.24–1.83)	1.94 (0.78–4.82)	0.75 (0.18–3.06)	1.35 (0.62–2.95)
≥65 years	1.19 (0.52–2.69)	0.99 (0.41–2.43)	1.09 (0.59–2.03)	0.83 (0.31–2.24)	1.27 (0.56–2.89)	1.05 (0.55–2.00)
Type of vaccine						
mRNA vaccines	0.74 (0.30–1.80)	0.90 (0.40–2.03)	0.81 (0.45–1.50)	1.28 (0.63–2.60)	1.12 (0.52–2.38)	1.21 (0.71–2.05)
Viral vector vaccines	1.57 (0.38–6.54)	1.57 (0.38–6.54)	1.61 (0.57–4.55)	0.86 (0.12–6.35)	0.89 (0.12–6.51)	0.87 (0.21–3.66)
BNT162b2	0.50 (0.16–1.56)	1.02 (0.45–2.31)	0.75 (0.38–1.47)	1.25 (0.59–2.69)	1.26 (0.59–2.70)	1.27 (0.73–2.21)
ChAdOx1 nCoV-19	1.86 (0.44–7.81)	1.86 (0.44–7.81)	1.92 (0.67–5.53)	0.93 (0.13–6.83)	0.93 (0.13–6.83)	0.93 (0.13–6.83)
Calendar time						
Before March 10, 2021	0.53 (0.06–4.26)	1.50 (0.30–7.60)	0.91 (0.22–3.78)	2.32 (0.42–12.79)	1.31 (0.14–12.59)	2.38 (0.43–12.99)
After March 10, 2021	0.92 (0.41–2.09)	0.86 (0.38–1.96)	0.89 (0.49–1.60)	1.03 (0.48–2.19)	1.00 (0.47–2.14)	1.02 (0.58–1.76)
Study period restricted to time after vaccination	0.93 (0.43–2.00)	1.07 (0.52–2.20)	1.00 (0.58–1.72)	1.29 (0.65–2.54)	1.15 (0.56–2.36)	1.24 (0.74–2.06)

IRR incidence rate ratio, *CI* confidence interval.

after vaccination and by censoring on March 10, results were consistent with those of the main analysis (Table 2).

DISCUSSION

This self-controlled case series did not identify an increased risk of RVO in the 28 days following the first and second doses of COVID-19 vaccination. Subgroup analyses by type of vaccine, gender and age did not reveal any evidence of an association. The results were robust over-sensitivity analyses performed to assess potential notoriety bias and test the assumptions that RVO did not influence the likelihood of subsequent vaccination.

The negative results of our study are in contrast with the current evidence suggesting a direct relationship between RVO and COVID-19 vaccination [2–10]. However, published literature consists entirely of anecdotal reports, and no inference on the purported association can be drawn from those studies. The present analysis suggests instead that the occurrence of RVO following COVID-19 vaccination may have been coincidental rather than causal.

Within the context of the current pandemic, safety concerns regarding the risk of thromboembolic events following vaccination merit attention. Reports of unusual thrombotic events in relation to vaccination started appearing in late February 2021, resulting in temporary suspension of the use of the ChAdOx1 nCoV-19 vaccine in several European countries. Subsequently, a novel clinical syndrome characterized by thrombosis at atypical sites combined with thrombocytopenia occurring after vaccination with Ad26.COV2.S or ChAdOx1 was described [15–17]. Although there was a single case report of bilateral ophthalmic vein occlusion in the context of vaccine-induced immune thrombotic thrombocytopenia [18], large studies did not indicate RVO as a typical manifestation of this syndrome [17].

After a period of intense public debate on COVID-19 vaccine safety, several countries are planning to offer a second booster dose in the next autumn. Our findings provide timely information to guide clinical decision making and advise regulatory authorities involved in risk-benefit assessments. Of note, previous studies have shown that the risk of thromboembolic adverse events associated with the COVID-19 infection itself is higher than the risk from vaccination [11]. In parallel, retinal vascular changes were reported in association with COVID-19 infection, including an increased incidence of RVO [19–21]. Since vaccination provides approximately 90% protection against the infection, the benefits of vaccines far outweigh the risks.

To the best of our knowledge, this was the first study providing risk estimates for RVO after vaccination. The self-controlled case series study design had the major advantage of overcoming the potential confounding for all fixed characteristics. Another strength of the study was the use of prospectively recorded, individual-level clinical data with ascertainment of cases through manual review of retinal images, which minimized concerns over the risk of recall and selection biases.

However, we also acknowledge limitations to this study. The main one was related to the relatively low number of cases, which reduced the precision of our estimates. In addition, some potential confounders such as systemic comorbidities could not be retrieved due to the retrospective nature of the study. Another limitation was the inclusion of multiple vaccine types in the main analysis. Although we performed vaccine-specific subgroup analyses, the number of cases in the subgroups was considerably lower, particularly for the mRNA-1273 and Ad26.COV2.S vaccines. Since we cannot exclude a small increase in risk due to the wide confidence intervals, our findings would benefit from validation from further studies using larger datasets. Nevertheless, it remains clinically relevant that we did not find any evidence of increased risk of RVO following COVID-19 vaccination. Finally, public concerns over vaccine-related thrombotic events may have led to increased care-seeking behaviour in vaccinated patients and increased attention in ophthalmologists. However, this would

have inflated the association between RVO and vaccination, and our negative results rule out the importance of such bias.

In conclusion, this study does not support an association between COVID-19 vaccination and RVO. As we await more epidemiologic data, our findings provide valuable information regarding the safety of vaccination, which can ease the anxiety of vaccine-hesitant patients, inform health professionals actively engaged in vaccine counselling and engender a greater level of public trust on COVID-19 vaccines.

Summary

What was known before

- Recently, there have been anecdotal reports of retinal vein occlusion following COVID-19 vaccination.

What this study adds

- In this self-controlled case series including 210 patients seen in five tertiary referral centres in Italy, no increased risk of retinal vein occlusion was observed after COVID-19 vaccination.
- The findings of this study suggest that COVID-19 vaccination is not associated with retinal vein occlusion.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Konstantinides SV. Thrombotic complications of vaccination against SARS-CoV-2: what pharmacovigilance reports tell us - and what they don't. Eur Respir J. 2021;58:2101111.
2. Tanaka H, Nagasato D, Nakakura S, Tanabe H, Nagasawa T, Wakuda H, et al. Exacerbation of branch retinal vein occlusion post SARS-CoV2 vaccination: Case reports. Medicine. 2021;100:e28236.
3. Bialasiewicz AA, Farah-Diab MS, Mebarki HT. Central retinal vein occlusion occurring immediately after 2nd dose of mRNA SARS-CoV-2 vaccine. Int Ophthalmol. 2021;41:3889–92.
4. Endo B, Bahamon S, Martínez-Pulgarín DF. Central retinal vein occlusion after mRNA SARS-CoV-2 vaccination: A case report. Indian J Ophthalmol. 2021;69:2865–6.
5. Girbardt C, Busch C, Al-Sheikh M, Gunzinger JM, Invernizzi A, Xhepa A, et al. Retinal Vascular Events after mRNA and Adenoviral-Vectored COVID-19 Vaccines-A Case Series. Vaccines. 2021;9:1349.
6. Peters MC, Cheng SSH, Sharma A, Moloney TP. Retinal vein occlusion following COVID-19 vaccination. Clin Exp Ophthalmol. 2022;50:459–61.
7. Pur DR, Catherine Danielle Bursztyn LL, Iordanous Y. Branch retinal vein occlusion in a healthy young man following mRNA COVID-19 vaccination. Am J Ophthalmol. 2022;26:101445.
8. Sugihara K, Kono M, Tanito M. Branch Retinal Vein Occlusion after Messenger RNA-Based COVID-19 Vaccine. Case Rep. Ophthalmol. 2022;13:28–32.
9. Sacconi R, Simona F, Forte P, Querques G. Retinal Vein Occlusion Following Two Doses of mRNA-1237 (Moderna) Immunization for SARS-Cov-2: A Case Report. Ophthalmol Ther. 2022;11:453–8.
10. Sonawane NJ, Yadav D, Kota AR, Singh HV. Central retinal vein occlusion post-COVID-19 vaccination. Indian J Ophthalmol. 2022;70:308–9.
11. Hippisley-Cox J, Patone M, Mei XW, Saatci D, Dixon S, Khunti K, et al. Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study. BMJ. 2021;374:n1931.
12. Farrington CP, Nash J, Miller E. Case series analysis of adverse reactions to vaccines: a comparative evaluation. Am J Epidemiol. 1996;143:1165–73.
13. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ. 2016;354:4515.
14. Farrington P, Whitaker H, Weldeselassie YG. Self-controlled case series studies: a modelling guide with R. 2nd edn. Boca Raton, FL: Chapman and Hall/CRC Press; 2018.
15. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N. Engl J Med. 2021;384:2092–101.
16. 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. 2021;384:2124–30.
17. Pavord S, Scully M, Hunt BJ, Lester W, Bagot C, Craven B, et al. Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis. N. Engl J Med. 2021;385:1680–9.
18. Bayas A, Menacher M, Christ M, Behrens L, Rank A, Naumann M. Bilateral superior ophthalmic vein thrombosis, ischaemic stroke, and immune thrombocytopenia after ChAdOx1 nCoV-19 vaccination. Lancet. 2021;397:e11.
19. Invernizzi A, Torre A, Parrulli S, Zicarelli F, Schiuma M, Colombo V, et al. Retinal findings in patients with COVID-19: Results from the SERPICO-19 study. EClinicalMedicine. 2020;27:100550.
20. Ullah I, Sohail A, Shah M, Khurshid M, Diwan MN, Qadir A, et al. Central Retinal Vein Occlusion in patients with COVID-19 infection: A systematic review. Ann Med Surg. 2021;71:102898.
21. Modjtahedi BS, Do D, Luong TQ, Shaw J. Changes in the Incidence of Retinal Vascular Occlusions After COVID-19 Diagnosis. JAMA Ophthalmol. 2022;140:523–7.

AUTHOR CONTRIBUTIONS

All authors contributed significantly to the creation of this manuscript; each having fulfilled criteria as established by the ICMJE.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Marco Pellegrini.