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Clotting Disorders After ChAdlx1 nCov-19 Vaccination Against COVID-19

Trastornos de coagulación después de la vacunación ChAdlx1 nCov-19 contra la COVID-19

Henry Mejía-Zambrano[1,a], **Livia Ramos-Calsín**[1,2,b]

[1]School of Human Medicine, San Juan Bautista Private University, Lima, Peru
[2]Bachelor of Nursing, Directorate of Integrated Health Networks Lima Centro - MINSA, Lima, Peru

ORCID:
[a]https://orcid.org/0000-0001-7325-7796
[b]https://orcid.org/0000-0001-7004-9190

Corresponding author:
Livia Yolanda Ramos Calsín

Postal Address: Calle Joaquín Capelo 503 – SMP. Teléfono: 986674245.

Email: liv.ramosc@gmail.com

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Dear Editor

The Oxford-AztraZeneca vaccine (Chadlx1 nCov-19), prevents coronavirus 19 disease (COVID-19) in people over 18 years of age; in addition to being composed of another virus (of the adenovirus family) that was modified to contain the gene to produce a protein from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), being that the vaccine does not contain the virus itself and cannot cause COVID-19 disease (9). It has been shown to be very effective especially in preventing serious illness and death from COVID-19, even after the first dose, and the second dose of the vaccine should be given 4 to 12 weeks after the first dose, without replacing a second dose of any mRNA vaccine, according to the Committee for Human Medicines (CHMP) (9).

In early and mid-March 2021, several European countries stopped the vaccination campaign against COVID-19 with the Chadlx1 nCov-19 (AZD1222) vaccine from Oxford-AstraZeneca, following several reports of thromboembolic events that caused the death of some people who had received this vaccine (2). On March 18, 2021, after discussing the information on these complications, The European Medicines Agency (EMA) concluded regarding the Oxford-AstraZeneca vaccine that "the benefits still outweigh the risks despite a possible link with clots. rare blood cells with low blood platelets" after vaccination (1). This led several countries to restart vaccination with the Oxford-AstraZeneca COVID-19 vaccine, however, other countries such as Denmark, decided to await further examination of the possible relationship between the vaccine and thromboembolic events (3). Furthermore, to help national authorities make decisions on how to best use the vaccine in their territories, the EMA CHMP has analyzed more of the available data to put these very rare blood clots at risk in the context of benefits. of the Chadlx1 nCov-19 vaccine for different age groups and different infection rates in COVID-19 (9).

The focus was on cerebral cavernous venous sinus thrombosis (CVST), a rare condition with an incidence of 15 cases per million people each year. CVST is a cause of stroke that affects young people and women, with important risk factors such as pregnancy and hormonal contraception (4). The increase in CVST in Europe and United Kingdom, together with the total absence of cases after vaccination by Pfizer or Moderna, were concrete indicators that thrombosis complications were related to the Oxford-AstraZeneca vaccine. It was observed that those affected also presented thrombocytopenia that is not normally found in patients with CVST (7). On February 17, 2021, the EMA and the World Health Organization (WHO) began a descriptive study, which used spontaneous reports submitted to the EudraVigilance database, where there were 54,571 reaction documents, of which 28 were associated with thrombotic adverse reactions; In addition, 3 deaths were found that were related to pulmonary embolism; being these cases, extremely rare events; However, on March 18, 2021, the EMA Evaluation Committee concluded that the Chadlx1 nCov-19 vaccine was safe, effective and that the benefits outweighed the risks (10).

On March 19, 2021, 13 cases of cerebral or sinus vein thrombosis were reported in Germany with more than 1.6 million doses of AstraZeneca COVID-19 vaccine administered; furthermore, these patients had a syndrome similar to heparin-induced thrombocytopenia (HIT), suggesting an immunological event as one of the possible origins of the thrombosis (10).Also, on April 7, 2021, during the conclusion of the EMA, several cases of thrombosis associated with thrombocytopenia were reported after the AstraZeneca vaccine, including arterial and splanchnic venous thrombosis (5). In one study, a case series of 11 patients with thrombosis associated with thrombocytopenia was found, the majority were women and the mean age was 36 years. From 5 to 16 days after Chadlx1 nCov-19 vaccination, patients had one or more thrombotic episodes, with the exception of 1 patient who had a fatal intracranial hemorrhage event. Of the patients with one or more episodes of thrombotic events, 9 had cerebral venous thrombosis, 3 patients had splanchnic thrombosis, 3 patients had pulmonary embolism, and 4 patients had other thromboses; of these patients, 6 died. None of the patients received heparin before the onset of symptoms. All 28 patients who tested positive for PF4-heparin antibodies tested positive for platelet activation in the presence of heparin-independent PF4. Platelet activation was inhibited by high levels of heparin (6) (Table 1).

Table 1. Clinical and laboratory summary of 11 patients with available clinical information. Prepared from Greinacher A and et al (6)

Variable	Patient Number										
	1	2	3	4	5	6	7	8	9	10	11
Platelet nadir (per mm 3)	13 000	107 000	60 000	9 000	23 000	75 000	29 000	16 000	13 000	8 000	NA for death
CVT	sí	No	sí	sí	sí	sí	sí	sí	sí	sí	Pending †
Splanchnic vein thrombosis ‡	sí	No	No	No	sí	No	No	No	No	sí	No
Pulmonary embolism	sí	sí	No	No	sí	No	No	No	No	No	No
Other thromboses	Aortoiliac	No	No	No	Right intraventricular, iliofemoral vein, IVC	No	No	Disseminated microvascular (brain, lungs, kidneys) §	Multi-organ thrombi §	No	Cerebral haemorrhage †
Onset of symptoms (number of days after vaccination)	5	6	9	7	13	7	8	8	16	11	12 ¶
INR Peak	1,40	1.12	N / A	1,66	1,25	1.05	1,34	N / A	1,70	N / A	N / A
Peak PTT (sec)	41,6	29,0	N / A	46,6	64,8	23,0	45,0	N / A	46,1	N / A	N / A
d-dimer peak (mg / liter)	142,0	1.8	13,0	N / A	N / A	2.6	> 33,0	N / A	21,0	> 35,0	N / A
Fibrinogen Nadir (mg / dl)	78	568	N / A	N / A	173	N / A	210	N / A	40	80	N / A
ELISA PF4-heparin (optical density)	3,16	3,08	3,50	3,40	1,20	N / A	N / A	2.02	3,51	2,35	2.16
PF4-dependent platelet activation assay	Pos	Pos ‖	Pos	Pos	Pos	N / A	N / A	Pos	Pos	Pos	Pos
Heparin treatment	sí	HBPM **	Unknown	sí	sí	Unknown	sí	No	No	No	No
Other medical condition	No	No	No	CND	VWD-I; FVL ACL-Abs	No	No	No	No	No	Unknown
Get out	Fatal	Recovery	Unknown	Fatal	Recovery	Recovery	Recovery	Fatal	Fatal	Fatal	Fatal

* Data are listed for the first four patients (including the index patient) who were evaluated and who had detailed laboratory results and for another seven patients who had fatal thrombocytopenia, thrombosis, or bleeding and for whom clinical information was available. One of the 11 patients was taking an oral contraceptive; two other patients had a hormonal intrauterine device. ACL-Abs denotes anticardiolipin antibodies, CND chronic neurological disorder, cerebral vein (sinus) thrombosis CVT (indicating presence of cerebral vein thrombosis, sinus thrombosis, or both), ELISA enzyme-linked immunosorbent assay, FVL Leiden factor V, INR international normalized ratio, IUD intrauterine device, IVC inferior vena cava, LMWH low molecular weight heparin, NA not available.

† Brain neuropathological findings were pending at the time of this report; CVT had not been ruled out.

‡ Splanchnic vein thrombosis indicates portal, mesenteric, splenic, or hepatic vein thrombosis.

§ These were post mortem findings.

¶ This is the day the body of the deceased was found.

‖ The sample that had an initial negative result in the PF4-enhanced platelet activation assay was subsequently shown to be positive when tested with other platelet donors.

** Low molecular weight heparin treatment was associated with clinical improvement and increased platelet count (107,000 to 132,000 over a 3-day period). The patient was then switched to direct oral anticoagulant when ELISA showed positive results for PF4-heparin antibodies, with greater clinical and platelet count recovery.

The UK Medicines and Health Products Regulatory Agency received 79 reports of thrombosis associated with low platelet levels, of which 44 were CVST. Of these 79 cases (13 serious), 51 were women and 28 (6 serious) men, presented the symptoms of thrombosis after the first dose of the AstraZeneca vaccine, the risk being in the younger age groups (7). There is still much that we do not know about thrombosis potentially linked to vaccination against SARS-CoV-2 and much of the information used by regulatory authorities was not made public (8). The regulatory agencies of the European Union and the United Kingdom acted effectively to the negative events raised, but they must publish not only their conclusions, but also the data and analysis of their conclusions (7).

It still remains true that the benefits are greater than the complications of the AstraZeneca vaccine, in the different adult age groups. Study findings should be interpreted with caution, as underreporting coupled with reporting biases can limit the generality of the findings. It is difficult to determine a causal effect of the vaccine on the causal effect of the vaccine on the number of reported diseases. A clear causal effect and factors and multiple causes of thrombotic events that were not reported or reported cannot be confirmed. More research is required to advise governments and the general population on the vaccination processes of Chadlx1 nCov-19.

Authors' contribution

All authors participated in the entire research process.

Conflict of interests

The authors declare that they have no conflicts of interest or with institutions or other authors.

Founding

The present study had no sources of founding.

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