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Resistance towards ChadOx1 nCoV-19 in an 83 Years Old Woman Experiencing Vaccine Induced Thrombosis with Thrombocytopenia Syndrome

Gillot, Constant; FAVRESSE, Julien; Maloteau, Vincent; Mathieux, Valérie G.; Dogné, Jean-Michel; MULLIER, Francois; Douxfils, Jonathan

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Methods for Assessing Resistance to Non-Integrating Virus Vectors

Constant Gillot¹, Julien Favresse^{1,2}, Vincent Maloteau¹, Jean-Michel Dogné¹, François Mullier^{1,3} and Jonathan Douxfils^{1,4} ¹Department of Pharmacy, Namur Research Institute for Life Sciences, University of Namur, 5000 Namur, Belgium ²Department of Laboratory Medicine, Clinique St-Luc Bouge, 5000 Namur, Belgium ³Université catholique de Louvain, CGU UCL-Namur, Department of Laboratory Medicine, B-5300, Yvoir, Belgium ⁴Qualiblood s.a., 5000 Namur, Belgium

INTRODUCTION

The use of adenoviruses for the development of vaccines has been known for almost 20 years [1]. The use of these viral vectors is ideal for vaccine therapy due to their ability to induce innate immunity and adaptive immunity in the host. In this case-report, we further investigate the case of an 83-year-old woman vaccinated with **ChadOx1 nCoV-19** who developed a vaccine-induced thrombosis with thrombocytopenia syndrome (TTS). Interestingly, on top of her TTS, she did not develop an antibody response against the spike protein of SARS-CoV-2 following the administration of her first dose of ChadOx1 nCoV-19.

METHODS

A **cellular model** for assessing resistance to the ChadOx1 nCoV-19 in the Vaxzevria® vaccine was developed. This test is based on the detection of the production of the spike protein (S protein) induced by ChadOx1 nCoV-19 (lot number: ABW4805) in the supernatant fraction of cells transfected by the

RESULTS

The controls all have positive anti-SARS-CoV-2 S protein antibodies titers with a mean titer of 2427 AU/mL (95% CI: 1581 AU/mL–6434 AU/mL) and negative anti-NCP antibodies titers. The results for the serum analysis of the patient not responding to Vaxzevria® are presented in **Table 1**. Table 1

Sample Dilution Factor	Sample D0 Absorbance	Sample D1 Absorbance
1/4	0.07	0.07
1/8	0.07	0.07
1/16	0.06	0.08
1/32	0.06	0.08
1/64	0.06	0.07
1/128	0.08	0.06
1/256	0.07	0.06
1/512	0.08	0.08
1/1024	0.07	0.07

The absorbance does not vary according to the serum dilution and

adenovirus vector (**Figure 1**).

Figure 1



The model is then exposed to the serum of the tested patient.

In presence of elements impairing the infection of the cells by ChadOx1 nCoV-19 as **anti-adenovirus antibodies** or other elements present in the serum to prevent the action of the adenovirus, the production of the S protein in the supernatant is reduced or abolished.

A549 cells (human lung adenocarcinoma cell line) were dispensed into a 24well plate at an optimal concentration to achieve confluence without excessive cell death. This cell mat was then placed with a fixed amount of ChadOx1 nCoV-19 vaccine and a progressive dilution of the patient's or control's serum.

The plate was then left for 7 days at 37 $^{\circ}$ C and 5% of CO₂ in a calibrated incubator. Measurement of the amount of S protein present in the supernatant after 7 days of incubation was performed using ELISA

remains between 0.06 and 0.08. These values were below the limit of quantification (LOQ) of the ELISA assay (LLOQ = 2 ng/mL). The results obtained with the controls provide mean concentrations for the different serum dilutions ranging from 21.60 ng/mL (95% CI: 17.20 ng/mL-26.00 ng/mL) to 24.52 ng/mL (95% CI: 17.23 ng/mL-31.81 ng/mL). (**Table 2**) Table 2

Sample Dilution Factor	VAXZEVRIA Double-Vaccinated Patients Mean Concentration (ng/mL)
1/4	24.52 (95% CI: 17.23–31.81)
1/8	23.36 (95% CI: 17.00–29.71)
1/16	24.28 (95% CI: 17.21–31.35)
1/32	21.98 (95% CI: 14.82–29.13)
1/64	22.71 (95% CI: 14.24–31.19)
1/128	22.81 (95% CI: 16.15–28.99)
1/256	22.57 (95% CI: 16.15–28.99)
1/512	21.60 (95% CI: 17.20–26.00)
1/1024	24.06 (95% CI: 18.16–29.96)
Overall mean (ng/mL)	23.10 (95% CI: 22.31–23.89)

CONCLUSION

Based on the results obtained, it can be assumed that the clinical case presented in this paper developed a form of **resistance against the adenovirus used in the ChadOx1 nCoV-19 vaccine**. The origin of this



Figure 2



resistance is still unknown, but this test allows to eliminate a possible lymphocytic or myelocytic origin.

The model developed is applicable to **other therapies** using adenoviruses vector such as anti-cancer therapies or several vaccines already on the market such as Ebola vaccine (Zabdeno®) or other COVID-19 vaccine as the Johnson & Johnson vaccine (Jcovden®).

In addition to these therapies already on the market, several studies are underway to develop a malaria vaccine based on adenoviruses such as Ad35 or Ad26.

The test developed would therefore make it possible to **assess an individual's resistance to an adenovirus-based therapy** more widely. This would make it possible to prevent the use of certain therapies that we know will not work in a particular individual. Importantly, a link with the TTS developed by our patient cannot be excluded and deserved further investigations

CONTACT INFORMATION

Constant Gillot

patent: EP22150499.6

<u>Constant.gillot@unamur.be</u> + 32 (0)81 72 42 92

