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Antibody response induced by the boost overdose during COVID-19 heterologous prime-boost vaccination strategy

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ABSTRACT

Background: Measurement of anti-SARS-CoV-2 RBD Ig G antibody response is very important to define the dynamics of immunization in vaccine COVID-19 recipients.
Materials and methods: Sera from four BNT162b2 vaccine recipients who erroneously received vaccine overdose were analyzed at different time-points.
Results: At 6 days the serum increase of antibodies was analogous for the three SARS-CoV-2 naïve recipients. At 14 days the antibody level increased and reached a peak, though showing a different pattern among the three recipients. At 21 days the serum antibody level started to decrease from its maximum value. The data for the previously infected recipient were in agreement with values found in COVID-19 positive receivers. Thus, the prime-dose of vaccine was enough to elicit a significant antibody response.
Conclusions: In spite of the overdosage, this study confirms the efficiency of the BNT162b vaccine in eliciting a sustained antibody response as heterologous boost-vaccine in previously Oxford/AstraZeneca vaccinated recipients, as well as, prime-vaccine in COVID-19 infected receivers. Importantly, the humoral immune response of recipients was not proportional to the vaccine overdose. Nonetheless, we cannot portray a univocal effect of vaccine overdose concerning anti-SARS-CoV-2 antibody response because the values found were highly heterogeneous.

1. Introduction

Due to the ongoing COVID-19 pandemic, vaccination continues to be critically important because it is regarded as safe and effective means to prevent disease and reduce virulence [1,2]. In order to boost the vaccination rate some different strategies have been proposed such as splitting the doses, delaying the second dose, heterologous vaccination and postponement of vaccination in seropositive recipients [3]. In addition, a practical problem with some types of vaccines is the multi-vial dose format and the need of preparation before administration, whereby its contribution to vaccine wastage (sum of vaccines discarded, damaged and lost) must be reduced. For vaccines that require two injections, healthcare organizations have typically recommended the second shot to be the same as the former. Following safety issues, mostly related to cases of atypical venous thrombosis, some European countries have decided to stop the use of the adenovirus-based Oxford/AstraZeneca vaccine. Consequently, millions of people were unable to receive a second dose of such vaccine, remaining only partially vaccinated. To resolve this matter, mix-and-match vaccine studies have been planned aimed to investigate the safety and immune response in people receiving two different types of COVID-19 vaccine [4,5]. Some preliminary studies carried out in different countries suggest that combining different vaccines induces potent immune response [6–9], but some safety concerns still remain [10]. On the other hand, although millions of COVID-19 vaccines have been administered around the world, in some cases vaccine overdoses have occurred, mostly due to human errors relating to the use of "multi-dose" vials [11]. These containers are useful in a pandemic situation because they allow a cheaper and more efficient distribution. However, multi-dose vaccines, mainly when the vaccine needs to be reconstituted before injection, are more prone to administration errors.

Abbreviations: BAU, Binding antibody units; CMIA, chemiluminiscent microparticle immunoassay; Ig G, Immunoglobulin class G; NHP, Non-human primates; RBD, Receptor-binding domain; $T_{6,14,21}$, Time-points; VORs, Vaccine overdose recipients.

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Table 1
Concentration of anti-SARS-CoV-2 RBD Ig G (BAU/mL) at different time points.

Recipient number	Time elapsed from Pfizer/BioNTech vaccine administration		
	T_6 = 6 days	T_{14} = 14 days	T_{21} = 21 days
VOR-1	780 (39)	1250 (63)	1040 (52)
VOR-2	690 (34)	2600 (132)	1930 (96)
VOR-3	680 (34)	6500 (324)	5000 (253)
VOR-4	1370 (68)	5500 (274)	4300 (214)

(): standard deviation values

For example, the Pfizer/BioNTech BNT162b2 mRNA COVID-19 vaccine (ComiRNAty) has been designed to be given in two 30 μg doses, 21 days apart [12]. Specifically, each single vial of this vaccine contains multiple doses (between five and six, in general). The active component of the vaccine (0.45 mL) must be diluted using 0.9% sodium chloride (1.8 mL). As a consequence, dosing errors may be caused by omitting the mandatory dilution by healthcare operators, so that a concentrated (higher dosage) product could be mistakenly injected.

Finally, one more controversial subject is the anti-SARS-CoV-2 serological monitoring of COVID-19 vaccinated population [13]. Therefore, the main purpose of this study was to report the anti-SARS-CoV-2 receptor-binding domain (RBD) immunoglobulin class G (Ig G) antibody response in recipients of erroneous Pfizer/BioNTech vaccination schedule (overdosage).

2. Material & methods

2.1. Ethical statement

All participants provided written informed consent to publish their analytical antibody values. The study complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration regarding ethical conduct of research involving human subjects.

2.2. Vaccine recipients

This four-case study was based on two males and two females, aged between 42 and 53 years. All this four vaccine overdose recipients (VORs) received 0.3 mL of the undiluted multi-dose vial, that means a vaccine dose increased by 5-fold (150 μg). Three recipients (VOR-1, 2 and 3) had no previous evidence of infection and received the first shot of Oxford/AstraZeneca vaccine 14.5 weeks before undergoing a second vaccination with Pfizer/BioNTech vaccine. The remaining subject (VOR-4) who had been previously infected by SARS-CoV-2 only received a single dose of Pfizer/BioNTech vaccine. Venous blood was taken at three different time points, i.e. 6 (T_6), 14 (T_{14}) and 21 days (T_{21}) after the administration of the Pfizer/BioNTech vaccine.

2.3. SARS-CoV-2 RBD Ig G antibody measurement

Abbott SARS-CoV-2 Ig G Quant® assay was used in this report as methodology for the quantitative assessment of anti-SARS-CoV-2 Ig G antibodies using the Architect platform (Abbott Laboratories Abbott Park, IL, USA). This is an automated two-step chemiluminiscent microparticle immunoassay (CMIA) designed to detect specific Ig G antibodies to the RBD of S1 subunit of SARS-CoV-2 spike protein [14]. All samples were processed by in accordance with manufacturers' instructions. Results of this assay are arbitrary expressed as AU/mL. Samples are considered positive when the value is $\geq$ 50 AU/mL. After the first international standard for anti-SARS-CoV-2 immunoglobulin has been released the results for anti-SARS-CoV-2 antibodies testing shall be expressed as binding antibody units per milliliter (i.e., BAU/mL) [15–17]. For the immunoassay used in this study, the conversion for reporting values in harmonized units was as follows: BAU/mL = AU/mL * 0.142 [14,18]

3. Results

3.1. Humoral response

The results of the anti-SARS-CoV-2 RBD Ig G antibodies levels measured in the four VORs at the three time points are summarized in Table 1. Since the mean reason that prompted this study was the consequence of a human error, the serum basal values of anti-SARS-CoV-2 RBD Ig G antibodies before the administration of Pfizer/BioNTech vaccine are unavailable. Thus, the serum basal value (T_0) was arbitrarily set at 57 BAU/mL, in accordance with values found in previous studies [6,19]. After Pfizer/BioNTech vaccine administration, a similar increase of serum anti-SARS-CoV-2 RBD Ig G antibodies levels was recorded at the first time point (T_6), with an approximate increase in the T_6/T_0 ratio of around 12-fold. At this time the concentration value for the one shot vaccine recipient (VOR-4) was nearly double compared to prime-boost vaccine recipients (VOR-1, 2 and 3). During the following week after Pfizer/BioNTech vaccine administration (T_{14}), the antibody level increased and reached a peak, but following a quite different pattern among the three VORs. At this time, the T_{14}/T_6 ratio values were 1.6, 3.8, 9.5 and 4.0 for VOR-1,2,3 and 4, respectively, whilst the T_{14}/T_0 ratio values were 22, 46 and 114 for VOR-1, 2 and 3, respectively. Finally, the antibody level decreased from the maximum values achieved during the third week after the Pfizer/BioNTech vaccine administration (T_{21}). At the third time point, the T_{21}/T_{14} ratio values were on average of 0.78. Similarly, the T_{21}/T_0 ratio values were 18, 34 and 89 for VOR-1, 2 and 3, respectively. At this time point, the result for VOR-4 was similar to the highest value obtained for VOR-3, and considerably higher that the values recorded in VOR-1 and VOR-2. For VOR-4, the data trend was in keeping to those previous found in positive COVID-19 recipients in whom the single prime-dose of BNT162b2 vaccine induced an antibody response similar to a full prime-boost dose in naïve recipients [20,21].

3.2. Side effects

No major systemic side effects could be recorded after administration of vaccine overdose in VORs recipients. The most commonly reported systemic events were headache and general malaise. Also, in some cases, fever and tiredness were described. Additionally, mild/moderate pain at the injection site, lasting between 72 and 96 h, was the most frequently described local reaction in VORs after vaccine administration.

4. Discussion

Despite the limited number of subjects studied in the present report, their specific nature is an important novelty from the scientific perspective, that prompted us to describe these cases. Basically, the VORś immugenicity found in our study was compared with experimental values relating to COVID-19 vaccination studies available from the current scientific. It is important to highlight that antibody binding responses after immunization can be evaluated using different immunoassays with diverse readouts, which critically make difficulties regarding to the comparisons of datasets [17,18]. Firstly, Vogel and co-workers reported the preclinical development of two m-RNA based vaccine candidates (BNT162b1 versus BNT162b2) in non-human primates (NHP) as recipients [22]. They were intramuscularly injected with two different dose levels of vaccine (30 μg and 100 μg) at days 0 and 21. Compared to the 30 μg vaccine dose, the increase of anti-SARS-Cov-2 RBD Ig G increment was only 10% for the 100 μg dose at the maximum concentration level (day 28), and ranged between 25 and 33% throughout the 21–42 days' period, thus confirming that a 3-fold higher vaccine dosage does not elicit a similar considerable increase of humoral immunity. Secondly, Borobia and co-workers evaluated

Table 2
Concentration of anti-SARS-CoV-2 RBD Ig G (BAU/mL) reported in the literature.

Reference	Time elapsed from Pfizer/BioNTech second vaccine dose administration (days)				
	0	7	14	21	28
Abbot Quant-naïve [14]			2691		
previously infected	3127				
Perkmann et al. [18]	156				
Kontopoulou et al. [23]			2121		
Ontañon et al. [24]	176	2872	2947	2188	
Velasco et al.-naïve [25]	145				
previously infected	3162				
Zee et al. [26]	230				1643
Zipeto et al.-naïve [27]	238			2776	
previously infected	2859				

recipients only partially protected with a first dose of Oxford/AstraZeneca vaccine [6]. Humoral response showed a robust immune response in the form of anti-SARS-CoV-2 RBD Ig G regarding to the heterologous vaccination schedule. Unfortunately, the values cannot be comparatively evaluated because data obtained using Abbot-Quant® methodology, although expressed as BAU/mL, are in general lower than those reported by Roche-Elecsys® [18]. Lastly, even though published information on immunogenicity after full-dose vaccine administration is still limited and occasional, some experimental results from the literature as regards to the immune response after the second dose of BNT162b2 vaccine in a homologous schedule were evaluated [14, 18,23–27]. The required conditions for the comparative study of VORs data were identical methodology (Abbott-Quant®) and exact time point for blood sampling (±1 day). The values for specific antibodies concentration are summarized in Table 2. There are a few studies reporting the baseline value before receiving the second vaccine dose, which values ranged between 145 and 238 BAU/mL. At 14 and 21 days the values for naïve recipients ranged between 2121-2947 and 2188–2776 BAU/mL, respectively. At these time points the values can be considered as lower, similar and higher for VOR-1, 2 and 3, respectively. For VOR-4 the value at 21 days was also higher when compared to vaccine standard dose recipients. In addition, the kinetics in humoral response regarding to anti-SARS-CoV-2 RBD Ig G was different when compared to NHP recipients. In the case of VORs, the maximum values were achieved during the second week instead of the first one after the Pfizer/BioNTech vaccine administration.

5. Conclusions

All the VORs included in this report developed a significant humoral immunity between 6 and 21 days after vaccination. In spite of the overdosage, this study hence confirms the double efficiency of the BNT162b2 mRNA COVID-19 vaccine concerning to generation of anti-SARS-CoV-2 RBD Ig G antibody response induced as heterologous boost-vaccine in previously Oxford/Astra-Zeneca vaccinated recipients. But it also provides evidence as prime-vaccine in COVID-19 infected receivers. The humoral immunity responses for VORs were very heterogeneous considering that a similar vaccine overdose has been injected. The common evidence is limited to the fact that all the VORs achieved the maximum level of anti-SARS-CoV-2 RBD Ig G values at the second week after vaccination, and then decreased. Despite this similar trend, significant differences in concentration levels among recipients of this study do not permit to report an unequivocal effect of vaccine overdose. This is due to all theoretically possible individual results for antibody responses such as attenuated, averaged and increased levels were stated.

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CRediT authorship contribution statement

Francisco Raposo: Conceptualization, Investigation, Writing – original draft. **Giuseppe Lippi:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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