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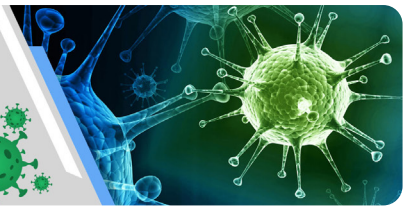

Dealing with COVID-19 Vaccine Related Antibody-Dependent Enhancement: A Mini Review

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Abstract

Antibody-dependent enhancement (ADE) is an antibody-mediated increase of infection which is a paradoxical reaction of the immune system during viral infection, when generally non-neutralizing antibodies facilitate and exacerbate infection. The ADE phenomenon is well known in veterinary medicine. It is contraindicated to vaccinate sick animals with the Rotavec® vaccine (designed against a bovine coronavirus and a rotavirus). In humans, during SARS-CoV-1 infections, the S-protein epitope was shown to produce both neutralizing and ADE antibodies. Newly-infected patients were not considered vaccinated until 15 days after the second dose of vaccine. In these patients (considered unvaccinated (< 15 days)), the vaccine could be able to induce an increase in antibody levels, initially neutralizing at low concentration and/or facilitating. Indeed, the facilitating antibodies which appear two to three weeks after one dose of vaccine would therefore be present at the time of the second dose. In relation to these mechanisms, the vaccine could therefore facilitate contamination and induce severe forms in patients who had been vaccinated but were wrongly considered unvaccinated.

Keywords: Spike, COVID vaccine, COVID-19, Myocarditis, ADE, Antibody-dependent enhancement

Introduction

Antibody-dependent enhancement is an antibody-mediated increase of infection (ADE) which is a paradoxical reaction of the immune system during viral infection, when generally non-neutralizing antibodies facilitate and exacerbate infection. The ADE phenomenon is well known in veterinary medicine, and the risk of a paradoxical post-vaccination exacerbation has already been raised [1]. It is contraindicated to vaccinate sick animals with the Rotavec® vaccine (designed against a bovine coronavirus and a rotavirus) [2]. In humans, during SARS-CoV-1 infections, the S-protein epitope was shown to produce both neutralizing and ADE antibodies, and this was convincingly demonstrated by comparing sera responses and anatomopathological findings in lungs between vaccinated rhesus macaques and patients [3]. The ADE phenomenon has been evoked for the Covid-19 vaccine but it was refuted [4]. However, we think that the reasoning underlying the rebuttal of the possibility of an ADE effect for Covid-19 is questionable, which some authors argue also [5, 6].

Firstly, the ADE phenomenon requires the presence of infected macrophages and circulating antibodies at the time of vaccination [7, 8]. Three main types of antibody-mediated ADE can be distinguished: (a) receptor-dependent ADE of infection in macrophages, (b) receptor-

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independent ADE of infection in other cells, and (c) receptor -dependent ADE of cytokine production in macrophages [9]. It should be remembered that Covid-19 vaccination was carried out worldwide during an epidemic period, and that no pre-vaccination tests were carried out on patients, nor was there any clinical examination to determine whether they had or already had the disease. This was a mass vaccination campaign during a phase 3 trial, with conditional marketing authorization and subsequent responsibility transferred from the laboratories to the States.

As it is the case with any drug, assessing the benefit-risk ratio of a vaccine is crucial. The COVID-19 vaccine transfection through body tissues distant from the injection site can cause numerous adverse effects, thrombosis and myocarditis in the first instance (the so called "spikeopathy") [10]. The potential carcinogenic effect as well as prion-like properties of the spike protein have not been studied [11]. Prion disease such as Creutzfeldt-Jakob disease, for example, can have a short incubation period (around one year), or a very long one (sometimes up to 40 years). The incubation period depends on the size of the inoculum and is shorter when a large number of prion proteins are inoculated [12]. Yet, potentially a very large number of spike proteins are inoculated by the vaccine, especially as the RNA used is modified to be more stable over time than natural RNA. Furthermore, vaccine RNA does not remain at the injection site, but spreads throughout the body, including the brain [13]. This means that incubation times could be very short, far less than a year, about 11 days in the cases of CJD subsequent to Covid-19 injection [14]. The virus and its spike protein could also be involved in accelerating senescence [15, 16].

The vaccine used to try and prevent the disease has a singular feature compared with other conventional vaccines. It does not involve the direct inoculation of a viral protein, but its manufacture by the human cellular machinery via the injection of mRNA. Cells, as in the disease, can thus express the spike protein on their surfaces [17], explaining the occurrence of myocarditis by a subsequent attack from the immune system. As cardiomyocytes are not equivalent to Antigen presenting cells (APC, like Dendritic cells), they cannot perform the essential antigen processing steps crucial for the correct presentation of the antigen to the lymphocytes that is immunization while preserving self-tolerance [18]. mRNA may also be directly involved. Vaccine-induced cytokine changes could also promote the onset of myocarditis [19-22]. Indeed, compared to nonvaccinated patients, asymptomatic patients who received their vaccination showed increased myocardial FDG uptake on PET/CT [23]. In addition, the direct toxic effects of the spike protein produced against the vascular endothelium which strongly expresses ACE2, the spike's target receptor, lead to inflammation, hypercoagulability and thrombosis [24]. This is clinically expressed in myocardial infarction, cerebral thrombophlebitis and stroke [25, 26]. It is crucial to note that myocarditis has already been described in the literature in the context of thrombotic thrombocytopenic purpura, a thrombosis-inducing disease that can occur in the aftermath of an endothelial aggression and subsequent dysfunction. These remaining adverse effects are difficult to assess. Most have not been reported to the authorities, partly because some doctors have peremptorily stated that these events were not related to the vaccine.

Analysis of the IHU Méditerrannée data on vaccination showed, among other results, the capacity of the Covid-19 vaccine to worsen the Covid-19 disease condition in some cases of severe underlying chronic illness, in the elderly patients and when the disease severity necessitated hospital admission. Additionally, sensitivity analysis showed that vaccination had no efficacy below 50 years of age [27]. Didier Raoult reported in his recent book an increased incidence of cases immediately after the vaccine injections [28]. The increase in the number of infections immediately after injection has not been the subject of comparative studies, and therefore of publications in scientific journals, but has been observed by many clinicians. Interestingly, after an epidemic peak rapidly diminishing at the end of December 2020, contaminations increased again in January 2021, which corresponded to the beginning of vaccination. These patients had probably already had contact with the virus and/or were infected (or about to be), with antibodies already in their blood. These newly-infected patients were not considered vaccinated until 15 days after the second dose of vaccine [29, 30]. Nevertheless, in these patients (considered unvaccinated (< 15 days)), the vaccine was able to induce an increase in antibody levels, initially neutralizing at low concentration and/or facilitating. In fact, the facilitating antibodies would appear two to three weeks after one dose of vaccine [31], and would therefore be present at the time of the second dose (which should be administrated between 21 and 49 days after the first dose). In relation to these mechanisms, the vaccine could therefore: (a) facilitate contamination (we know that a minimal inoculum is necessary, and the vaccine would be thus able to reduce the size of this inoculum according to the presence of facilitating antibodies), and (b) induce severe forms (severe forms counted as part of the group of unvaccinated patients). It has been established that a low concentration of neutralizing antibodies (in the first few days post-injection) is a key factor in the development of ADE [1, 32]. In addition, vaccination of an already-infected subject can also promote an ADE through the creation of antibody (vaccine)-antigen (infecting virus) immune complexes [8]. It is worth mentioning that the vaccinal spike mRNA is quite different from the viral one, and this may impact the type of the antibody produced. The use of numerous 1-methyl-

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pseudo-uridines (1MPU) throughout the vaccinal sequences renders the conservation of the glycosylation sites impossible. Those differences in glycosylation - given the essential roles of post-translationally-added glycans in intracellular protein routing – lead to distinct processing pathways [33], which are bound to have yet-unknown effects in the immune responses. The importance of those glycosylations is further confirmed by an in-depth analysis of the 22 N-linked glycans per spike monomer, expressed with ChadOx, which does not require 6MPU. Although able to claim the expression of the native form of the protein, there were still reported differences [34]. Changes in both N-linked and O-linked glycans were found between SARS-CoV2 and the main 5 variants (Alpha, Beta, Gamma, Delta, Omicron) and correlated with higher resistance to neutralizing antibodies [35]. Those circumstantial evidences indicate that Glycans may this play a role in antibody selection by the immune system.

Last but not least, a neutralizing antibody can become facilitating after a virus mutation. However, the vaccine was designed to neutralize the first Alpha strain of the virus, and not later variants such as Omicron [1, 24]. The modeling work published by Yahi et al. shows that antibodies facilitating the spread of the virus (ADE) have more affinity with the spike protein than with neutralizing antibodies in regard to the delta variant (on the contrary to what is observed with the original strain of SARS-CoV-2 of 2020, Wuhan/D614G) [36]. Furthermore, a facilitating epitope situated on the lower part of the N-terminal domain of the spike protein seem to be strongly conserved among most SARS-CoV-2 variants, which may represent a risk of ADE [37]. The problem of mutation occurrence, mutation-induced variants and paradoxical aggravations after re-infection or vaccination has been well described for dengue fever, Zika, Ebola, HIV, SARS-CoV, MERSCoV, and feline infectious peritonitis [38-45]. Surprisingly, it has not been the subject of much analysis nor discussion for Covid-19.

Importantly, a few clinical studies have shown real indications of ADE [39-41]. In a case report of a woman recently vaccinated (7 days) with mRNA BNT162b2 vaccine who died from ARDS, the authors consider the vaccine as responsible for the aggravation of COVID-19 [46]. There was no trace of COVID-19 infection, however anti-spike antibodies were found on day 13 after injection. In another study, 2 patients in COVID-19 acute phase were vaccinated with BNT162b2 (both on the 26th day of the illness) [47]. Both patients had COVID-19 pneumonia before receiving SARSCoV-2, and soon after vaccination had new ground-glass opacities and respiratory failure. The authors of this study suggest that this reaction was reactivated by vaccination. Also, autopsies of 170 people who died from COVID-19 (or carrying the virus at the time of death) showed lung viral loads much higher in vaccinated group (n=29) than in unvaccinated group (n=141) (45% vs. 16%, respectively P = 0.008) and it was more significant in the partially vaccinated (n=16). The authors do not exclude the role of ADE in this phenomenon [48].

On the other hand, patients who have not been infected within this short period (D1-15) may be part of a population that is more resistant to the effects of the virus, resulting in mild symptomatic forms. This bias could explain a measurable but artificial beneficial effect of the vaccine, which is in fact false if we take into account the entire post-injection period (before and after D15). It should also be noted that the number of sufferers increased considerably during the vaccination campaign, which could be linked not only to a mutation (appearance of the more contagious and less virulent omicron variant) but also to an ADE effect of the vaccine favoring infection. It is also possible that the vaccine increases contamination during the period when antibodies are at low concentration, and protects at another time, later when neutralizing antibodies are in sufficient concentration, for a given strain, in the case of Wuhan (the strain from which the vaccine was designed). As already mentioned, for mutants, an initially neutralizing antibody can become facilitating: the same reasoning cannot be applied to the Omicron strain.

Observation of peaks of Covid-19 contamination subsequent to mass vaccination initiation and the various immunological mechanisms mentioned above allow us to suspect the presence of ADE phenomena, or at least to seriously envisage their possibility. Our assertions have some limitations relating to Halstead and Katzelnick main argument that boils down to: “In contrast to dengue virus, SARS and MERS CoVs predominantly infect respiratory epithelium, not macrophages. Severe disease centers on older persons with preexisting conditions and not infants or individuals with previous coronavirus infections.” However, their argument that it was not epidemiologically nor pathologically observed is very weak in the light of the two signals factually observed : (a) the peak of contamination following mass vaccination initiation and (b) the results of statistical analysis of the IHU Méditerrannée data showing that vaccinated patient, without risk factors and comorbidities and with a disease condition necessitating hospitalization, had a statistically significant higher risk of experiencing ICU transfer or death compared with unvaccinated patients. Careful and systematic retrospective review of patient’s files could confirm our hypotheses, possibly taking into account the patient's evolution since the first day of injections.

In conclusion, the effect of Covid-19 mass vaccination may be compared to that of a pyromaniac fireman and nothing is less certain than that it has prevented an aggravated disease state in fragile patients who developed the disease despite vaccination. There is a need for evaluating the neutralization/

ADE balance of the variants following the initial virus in the sera of vaccinated individuals, especially in the frame of a mass vaccination campaign in order to adapt the vaccines to the most relevant and current variant. Some authors therefore strongly suggested that informed consents should disclose the specific risk of ADE and worsened COVID-19 disease from vaccination with separate form and demonstration of patient comprehension in order to meet medical ethics standards [49]. Vaccine efficacy in the general population should have been assessed without prejudice, for a given mutant, from the first day of injection, which obviously does not preclude later analysis when neutralizing antibodies have developed.

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