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The Coronavirus Vaccine and Risks of Antibody Dependent Enhanced Infections

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Review Article

Abstract:

Do SARS COV vaccines have the ability to sensitize people to antibody-dependent enhanced (ADE) breakthrough infections? The Corona virus disease in humans is lacking in not only the clinical and epidemiological features but also theimmunopathological aspects of an ADE illnessillustrated by dengue viruses (DENV), hence this is highly unlikely. While DENV invades macrophages, SARS and MERS COVID strainsmainlyattack the respiratory epithelium. People of old age and those with co morbidities like diabetes and hypertension are more vulnerable to the serious form of the COVID-19 infection. Neither infants nor individuals with previous coronavirus infections are high risk candidates for the severe form of this disease. Experiments conducted on animals given live SARS or MERS virus vaccines showed vaccine associated hypersensitivity reactions (VAH), much akin to the kindobserved in humans who were injected with the inactivated form measles or RSV vaccines. In order for the SARS COV vaccine to be safe, VAH must be avoided at all costs.

Keywords: Corona virus, SARS-CoV-2, dengue virus, dengue hemorrhagic fever, antibody-dependent enhancement (ADE) response, vaccine adverse reactions, vaccine, hypersensitivity,T cells immunopathology.

Introduction:

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2), a part of a group of viruses that can lead to serious illnesses in many animals, took the world by storm in 2020. The last time humans were afflicted with such a dangerous worldwide illness was the smallpox pandemic between 1870 and 1874 and the Spanish influenza in 1918. The

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antibody-dependent enhancement (ADE) is partly responsible for the difficulties in creating an effective vaccine against COVID 19. ADE is consisted of two phenomena of the immune system which are vaccine-centric: intrinsic ADE (iADE) and vaccine hypersensitivity (VAH).(1)The microbial pathogen and IgG antibody bind to form immune complexes which, on attachment to Fc receptors, not only bring about initiation but also promote replication of the microbe by bringing about suppression of the body's innate cellular defenses.(2) This is the mechanism of iADE. With the advent of formalin-inactivated measles vaccine in the US and European countries in the early 1960s, a significant number of children developed atypical measles, for which VAH was to blame. Several infants aged 4–12 months documented a vaccine-associated enhanced respiratory disease (VAERD) after being injected with a respiratory syncytial virus that was inactivated by the action of formalin. This was followed suit by infection with atypical RSV. Type hypersensitivity and/or an Arthus reaction caused such outcomes. On examination of the affected areas of the lung, an excess of neutrophils and eosinophils were found along with abundant macrophages and lymphocytes. After conducting studies on animals in laboratories, it was postulated that the viral antigens subjected to formalinled to a rise inabnormal antibodies that in turn led to polarization of T-helper 2 cells with further activation of humoral response and caused T-helper 1 cell suppression leading to a decrease in cytotoxic T lymphocytes (a part of cellular immunity).(3)When exposed to the wild strain of RSV, several mice that had formerly been exposed to RSV vaccines, showed a similar reaction. A pathological response much similar to VAH has been reported time and again in variouslive specimens in the lab that wereinjected with Severe Acute Respiratory Syndrome (SARS) and Middle East respiratory syndrome (MERS) Corona viruses, with as well as without anadjuvant.(4)Coombs type III antigen hypersensitivity is the most accurate way to define a VAH although it must be noted that there is no given proof that this response is interceded by antibodies. The exact technique of the disease enhancement that occurs after being vaccinated with the measles virus and its resemblance with VAERD are yet to be uncovered.

The hypothesis that ADE is a contributing factor to COVID-19 disease severity in humans can be attributed to experiments conducted on Fc receptor laden cells in vitro which showed an augmentation in SARS COV infection in the presence of human corona virus antibodies along with the behavioral pattern seen in non human species who were subjected to the Corona virus. (5)Firstly,elevatedamounts of SARS Corona Virus 1 Immunoglobulin G antibodies were reported in patients suffering from a serious form of SARS-CoV-1 infection. Secondly, the appearance of neutralizing IgG antibodies against the virus was seen much earlier in fatal cases as compared to the recovered cases. All this evidence points towards extensive tissue damage being due to ADE. When the sera from SARS or MERS vaccinated animals were added in vitro, it lead to the acceleration of COVID infections. Hence it was believed that the illnesses seen after being vaccinated were also triggered by ADE.(6)

Materials and methods

An extensive search was made on the website PubMed using the terms **Coronavirus, Covid19, SARS-CoV, vaccine, and adverse reactions** up to 8th February 2021. Furthermore, other established medical journals and websites were browsed as well.

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Discussion:

Coronavirus is a large group of RNA viruses that cause a variety of illnesses in vertebrates. In humans they usuallycan trigger respiratory infections, ranging frommild illnesses like coryza to grave illnesses such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). A new strain of coronavirus discovered in humans since an unforeseen event appeared in the city of Wuhan in China, in the month of December in 2019, was later named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV2), and clinically pioneered the infamous Coronavirus Disease-2019 (COVID-19).(7) COVID-19 is caused by SARS-COV2 which is a part of the identical group of coronaviruses as the etiological agent of SARS in 2003, only with different types of viruses. The symptoms are similar to SARS, but the mortality rate of SARS (9.6%) is higher than COVID-19 (less than 5%), although the number of cases of COVID-19 is far more than SARS. COVID-19 also has a wider and faster distribution to several countries than SARS.(8)Universally seen clinical manifestations includefever ≥38C, cough without expectoration, sore throat, and difficulty in breathing. If a person has travelled to a foreign nation(with COVID-19 cases) within a fortnight of the onset of symptoms, or has been in close connection with any patient suffering from the disease itself, then that person has to undergo certain virological tests to check whether he has contracted the viral disease or not.(9) Like other respiratory ailments, the SARS-CoV2 can inducesymptoms which can be managed at home with over the counter drugs. These include runny nose, bouts of coughing without sputum, an itchy painful throat and general fatigue and muscle pain.A whopping percentage of 80% of affected persons experience a resolution of symptoms without the necessity for hospitalization or special medical interventions.(10)However, 1 in every 6 patients may develop lower respiratory tract features like pneumonia. They may experience pain in the chest and dyspnoea. While around 3% of the afflicted people succumb to this disease, it is noteworthy that persons of older age and comorbidities like coronary heart disease, diabetes mellitus and hypertension are highly susceptible and constitute the high risk group for this virus.(11)

Any person coming in contact with a patient who is currently infected with the coronavirus, can contract the disease himself/herself. The disease spreads via droplets which are secreted from the nasal or oral membranes. These tiny droplets can exit when a patient coughs, sneezes or spits. Apart from this, it is postulated that the droplets can contaminate objects and surfaces and can spread when a person touches such items and then proceeds to touch the eyes or the area in and around the nostril and the oral orifice. These are known as fomites.(12)

A standard treatment protocol of persons experiencing milder symptoms is purely based on the principle of symptomatic relief and prevention of secondary bacterial infection. NSAIDs like paracetemol are used to alleviate headache, fever and muscle ache.(13) Cetrizine and its analogs are used to treat coryza. Cough syrup was commonly prescribed to patients with sore throat and cough, along with betadine gargles. Azithromycin 500mg given twice daily was the standard drug prescribed by several physicians to those with upper respiratory tract symptoms in order to prevent secondary bacterial infections.(14) Immunity boosters in the form of vitamin C and zinc were also given. In the initial period it was believed that hydroxychloroquine was an effective drug to confer immunity against contracting the virus, although it is no longer being used in the prophylaxis of COVID-19.(15)

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Patients having lower respiratory tract involvement, often showed findings like a drop in the arterial oxygen saturation, bilateral fluffy exudates on XRAY and CT, as well as change in their coagulation profile. Most patients showed elevations in D-dimer. Acute phase reactants like ferritin were also raised. The erythrocytic sedimentation rate (ESR) as well as serum lactate dehydrogenase (LDH) also saw a spike.(16) Such patients were managed by securing their airway and providing O2 inhalation by devices like nasal prong, bag and mask and even ventilators in serious cases. Corticosteroids became the mainstay treatment of ARDS in order to bring down the inflammation in the lungs.(17) Recent innovations lead to the use of Remdesivir and Tocilizumab. Remdesivir is an anti-viral drug that prevents replication of viral RNA. Tocilizumab is a newly created monoclonal antibody that competed with interleukin-6 for its receptor and thus prevents IL-6 from being bound and thus prohibits the release of chemical inflammatory substances that activate the T and B lymphocytes. This was essential to control the cytokine storm which is hypothesized to be the reason for severe ARDS in patients with SARS CoV2.(18)

Dengue ADE

The epidemiology, immunology and symptomatology of dengue virus (DENV) should be similar to those in SARS or MERS cases in order to determine whether iADE affects the latter's outcome. In living tissue, iADE requires an immunological stimulus which initiates the entire process, termed sensitization. In dengue, this can take place in three varied ways. The first being the initial exposure to the causative infectious agent, second including the multitypic dengue antibodies that are transferred to infants from mothersand lastly vaccination which resulted in incomplete protective immunity.(19)The circulation of 4 antigenically related DENV strains is essential to trigger iADE. Once a person is first exposed to a DENV strain, there is a period of up to two years comprising of comparative cross-protection following which although homologous immunity remains intact, a heterotypic DENV infection may incitea serious form of dengue. Following the second infection, lifelong heterologous protection is granted to the individual. Any infection following this will not cause a pathological reaction. Viremia titers may peakrelatively early but in each successive infection, the duration and titers of viremia decrease.(20)

Dengue is among the most serious and widespread health problems globally. An estimated 2% risk of being hospitalized for enhanced dengue disease exists lifelong in certain countries where dengue is endemically present. Severe dengue virus iADE infections have a short duration with a characteristic clinical chronology that begins with a sudden onset of fever and generalized symptoms like malaise and fatigue which is followed by quick extravasation of fluid into the extracellular compartment, which results in anoxia, haemorrhage and shock. It was first observed that the dengue virusprimarily invaded the peripheral blood leukocytes (PBL) derived from monkeys and humans who had previously been infected with dengue virus but was not detected in PBLs from non-immune donors.(21) An experiment was conducted in which antibodies mediated an enhanced dengue infection in monkeys. This helped confirm the hypothesis that severe DENV infections in 5-11 month old infants were caused by the maternal antibodies passed on passively to the infants from immune mothers. If there is an early rise and peak in the dengue antibody titers, this is indicative of a serious form of dengue viral illness The monocytes, macrophages, and dendritic cells present in spleen and lymph nodes are major seats of infection by DENV as seen under the microscope in various histopathological slide studies.The viral protein (nonstructural protein 1 [NS1]) damages the endothelial glycocalyx in humans which

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consequentially leads to capillary damage and increased vascular permeability leading to loss of fluid. It is to be emphasized that this cascade of vascular events is not mediated by inflammatory cytokines but by the toxin produced by the virus itself.Dengue fever is a disease caused by the dengue virus which is mainly seen in tropical regions since the vector responsible for its transmission is the Aedes mosquito. Symptoms characteristically appear within two weeks after the virus is introduced into the body. A significant rise in body temperature, excruciating musculoskeletal pain and an erythematous skin rash are the main clinical features seen in infected individuals. People usually take 2-7 days to recover. Sometimes there is a risk of developing severe forms of this disease namely dengue hemorrhagic fever manifesting as bleeding, decreased thrombocyte count and leakage of fluid from the vascular compartment which can turn into dengue shock syndrome where there is lack of perfusion of organs and hypotension.(22) Humans are the primary host of the virus, but it is also detected in other primates. A female Aedes mosquito has a blood meal on a human prey and this single bite can inject the virus into the blood. Subsequently if another unaffected female mosquito sucks the blood of an infected person, this virus enters the gut and invades the epithelial tissue, thereafter spreading to the rest of the body of the insect. The salivary glands thus get contaminated as well and the virus is shed in the saliva. The virus seems to have no harmful effect on the mosquito, which remains in the mosquito's body for the rest of its life.(23)

SARS ADE

A demonstration of classic ADE disease is seen in cats infected with the corona virus, which predominantly afflicts the peritoneal macrophages causing feline infectious peritonitis (FIP).In kittens, a milder version of the disease is transformed into a fatal one by the maternal antibodies, which are passed on passively. Maternal antibodies that are passively transmitted to their offspring,lead to the conversion of FIPV infections in kittens from a mild disease to one with fatal outcome.(24)As opposed to this, SARS and MERS Coronavirus infections in humans have an affinity for respiratory tract tissues not the reticuloendothelial system. The leading cause of mortality in such patients is acute respiratory distress syndrome (ARDS).In the period of 2001–2003, among all the SARS-CoV-1 cases, the mortality rate was less than 1% in those under 25 years old, 6% among 25–44 year olds, 15% in those aged between 45 and 64 years, and over 50% in those individual older than 65 years. A similar pattern was recorded in aged based fatality rates in the recent COVID-19 pandemic. SARS-CoV-1 strain primarily affected the epithelial cells of the alveoli which lead to widespread damage to alveolar tissue caused directly by the virus itself, that resulted in cellular death(necrosis). This was followed by deposition of fibrin and hyaline in the alveoli along with penetration of the virus into alveolar macrophages and interstitial cells. Multinucleated giant cells were another feature seen in the alveoli. Although the virus also affected several other organs like the liver, intestine, sweat glands, kidneys, etc, very little histological evidence was seen to explain such damage.During the course of the illness, the intensity of infection kept increasing which was seen in the amount of SARS CoV 1 virus being shed in respiratory, intestinal and sweat secretions. The normal physiological period of change from IgM to IgG antibodies was recorded in such cases, however some cases showed raised IgG Abs even as early as 4 days after the onset of the disease. It is postulated that aproperly functional T lymphocyte immunity(cellular immune response) is necessaryto recover from SARS-CoV-1 infection.(25)

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While many properties are shared by SARS, MERS, and COVID-19 both clinically as well as pathologically, lungs from patients with COVID-19 show distinctive offense to the vascular endothelial lining along with the presence of the virus intracellularly which ultimately leads to destruction of the cell membrane. When the vessels in the lungs of patients suffering from COVID-19 virus were examined histologically, proof of widespread clot formation, damage to tiny capillaries and reactive formation of new blood vessels was discovered. While in dengue, the capillary damage was largely attributed to the viral toxin itself, in COVID-19 viral strain, the damage to vessels is believed to be due to inflammatory cytokines released by the body itself. This phenomenon is called "cytokine storm". Whether cytokines are the reason for the infection or merely the result of it, is hard to determine since their production is triggered by the virus invasion itself(26). Non-protective antibodies that develop after vaccination are thought to be responsible for the immunopathology of VAH. It was observed in several laboratory experiments, that animals injected with SARS and MERS corona virus vaccines, showed a post challenge VAH reaction. Furthermore, the monkeys that were exposed to SARS-CoV-1 virus had inflammatory changes in their lungs on being re-exposed to the homologous viral strain. The exposure of laboratory animals to the COVID-19 vaccine as well as studying the response of human volunteers vaccinated with live SARS-COV-2virus will help to understand the clinical and immunological behavior of the virus, test if the vaccine produces VAH and to determine if the vaccine can provide early or sustained protection against the virus. Direct infection of individuals post-vaccination would also be a helpful method to determine if the vaccine can provide a solid long lasting immune response. Considering how imperative it is to develop an effective vaccine to combat the COVID-19 virus, more focus should be kept on the VAH reactions associated with the vaccine. Many of the related articles reflect on various aspects of COVID-19 (27-29). Bawiskar et. al. hematological manifestations of COVID 19 (30). Hande et. al. reported about cytokine storm in severe COVID-19 infection (31).

Conclusion:

Alongside several others, Itoo conclude that the contrasting features in clinical, epidemiological, and pathological findings of the diseases caused by SARS Coronaviruses 1 and 2 and dengue viruspoint towardsthe statement that iADE is not a contributing factor to the severity of naturally acquired human coronavirus infections. While the dengue virus primarily infects the reticuloendothelial system including myeloid cells, the SARS CoV 1 and 2 viruses have an affinity for type II pneomocytes, bronchial epithelium and other parenchymal cells, as seen in various laboratory as well as autopsy studies. This is the reason why the non-protective antibodies against corona virus, derived from vaccine introduction, are not anticipated to produce iADE response in humans. When epidemiological studies were conducted on patients with Corona virus, it was found that there was no relation between severity of the disease and history of previousinfection.This is opposed to dengue viral infection cases, where a past infection age cluster was observed in Tahitian children aged 4-12 years in 2001. These children were sensitized to DENV2 in 1996-97 and consequently developed severe infections on exposure to DENV1 in 2001.The query regarding SARS and MERS Corona virus being able to grant a solid protective immunity still exists. It is seen in most viral infections of the respiratory tract that a superinfection by the same organism cannot be prevented. This can be exemplified by those individuals immune to measles and rubella viruses who were re-infected by the same.

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