Disclosure to vaccine trial subjects of specific risk of COVID-19 vaccines worsening clinical disease in informed consents

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Abstract

Aims of the study Patient comprehension is a critical part of meeting standards of informed consent in study designs. The aim of the study was to determine if extant literature exists to require clinicians to disclose the specific risk that COVID-19 vaccines could worsen disease upon exposure to challenge or circulating virus. Methods used to conduct the study Published literature was reviewed to identify extant preclinical and clinical evidence that COVID-19 vaccines could worsen disease upon exposure to challenge or circulating virus. Results of the study Based on the history of coronavirus vaccine development, COVID-19 vaccines designed to elicit neutralizing antibodies may sensitize vaccine recipients to more severe disease than if they were not vaccinated. Vaccines for SARS, MERS and RSV have never been approved, and the data generated in the development and testing of these vaccines suggest a serious mechanistic concern: that vaccines designed empirically using the traditional approach (consisting of the unmodified or minimally modified coronavirus viral spike to elicit neutralizing antibodies), be they composed of protein, viral vector, DNA or RNA and irrespective of delivery method, may worsen COVID-19 disease via antibody-dependent enhancement (ADE) of either infection or disease. Conclusions drawn from the study and clinical implications The specific and significant COVID-19 risk of ADE should have been and should be clearly and emphatically disclosed to research subjects currently in vaccine trials, as well as those being recruited for the trials and future patients after vaccine approval, in order to meet the medical ethics standard of patient comprehension.

TITLE: Disclosure to vaccine trial subjects of specific risk of COVID-19 vaccines worsening clinical disease in informed consents

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Methods used to conduct the study

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Results of the study

Based on the history of coronavirus vaccine development, COVID-19 vaccines designed to elicit neutralizing antibodies may sensitize vaccine recipients to more severe disease than if they were not vaccinated. Vaccines for SARS, MERS and RSV have never been approved, and the data generated in the development and testing of these vaccines suggest a serious mechanistic concern: that vaccines designed empirically using the traditional approach (consisting of the unmodified or minimally modified coronavirus viral spike to elicit neutralizing antibodies), be they composed of protein, viral vector, DNA or RNA and irrespective of delivery method, may worsen COVID-19 disease via antibody-dependent enhancement (ADE) of either infection or disease.

Conclusions drawn from the study and clinical implications

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What's known

There is extensive knowledge of the risk of ADE in prior viral epidemics of SARS, MERS and RSV, extensive knowledge about the molecular similarities between SARS, MERS and SARS-CoV-2, the causative agent of COVID-19, extensive knowledge about the pattern of COVID-19 disease in individuals and populations and extensive knowledge about the composition and design of SARS, MERS and COVID-19 vaccines.

What's new

Whether clinicians are specifically disclosing the risk of ADE to COVID-19 vaccine recipients in clinical trials, which portends the standard of care after vaccine approval, is unknown. Whether ADE will and has been occurring in COVID-19 remains unproven. This review reveals that the probability that ADE is occurring or will occur in COVID-19 and vaccine recipients is high enough to be significant, requiring disclosure as a specific risk in informed consents for COVID-19 vaccines.

Introduction

The elicitation of antibodies, preferably neutralizing antibodies, is the goal of nearly every current SARS-CoV-2 vaccine candidate, but emerging data suggests that severe COVID-19 disease is associated with the development of anti-SARS-CoV-2 serum antibodies[1]and that subjects who recover quickly have low or no anti-SARS-CoV-2 serum antibodies[2]. A recent study also revealed IgG-mediated acute lung injury *in vivo* in macaques infected with SARS that correlated with a vaccine-elicited, neutralizing antibody response[3]. Inflammation and tissue damage in the lung in this animal model recapitulated the inflammation and tissue damage in the lungs of SARS-infected patients who succumbed to the disease. The time course was also similar, with the worst damage occurring in delayed fashion in synchrony with ramping up of the immune response. Remarkably, neutralizing antibodies controlled the virus in the animal, but then would precipitate a severe, tissue-damaging, inflammatory response in the lung. This is a similar profile to immune-complex mediated disease seen with respiratory syncytial virus (RSV) vaccines in the past, wherein vaccinees succumbed to fatal enhanced RSV disease due to the formation of antibody-virus immune complexes that precipitated harmful, inflammatory immune responses. It is also similar to the clinical course of COVID-19 patients, who experience their most severe morbidity and mortality via inflammation in lung (including eosinophilic

pulmonary infiltrates), blood (coagulation), cardiac and other tissues at a delayed phase after symptomatic infection, when the antibody response is emerging but viral loads may be declining or absent. This picture, which is vertically consistent from controlled SARS studies in primates to clinical observations in SARS and COVID-19, suggests the risk that vaccine candidates composed of the SARS-CoV-2 viral spike and eliciting anti-SARS-CoV-2 antibodies place vaccinees at higher risk for more severe COVID-19 disease when they encounter circulating viruses.

Indeed, studies in mice of prior SARS vaccines revealed this exact phenotype, with four human vaccine candidates eliciting neutralizing antibodies and protecting against SARS challenge, but viral re-challenge of thus vaccinated animals resulting in immunopathologic lung disease[4]. Independently, SARS/MERS vaccine candidates, commonly exhibited antibody-dependent enhancement (ADE) associated with high inflammatory morbidity in preclinical models, obstructing their advancement to the clinic[5,6]. SARS ADE of both disease in non-human primates and viral infection of cells *in vitro* was clearly mapped to specific antibody-targeted SARS viral spike epitopes[7]. This phenomenon was consistent across a variety of vaccine platforms, including DNA, vector primes and virus-like particles (VLP), irrespective of inoculation method (oral, intramuscular, subcutaneous, etc). An unknown variable is how long this tissue damage lasts, possibly resulting in permanent morbidity (e.g. diabetes from pancreatic damage[8]).

Importantly, this *ADE of disease* , or immunopathology, that distinguishes the morbidity, and likely the case fatality rate, of SARS, MERS and COVID-19 disease from comparators, like influenza disease, may be pathophysiologically independent from *ADE of viral infection* . Both are anti-viral-antibody dependent, and the latter can be measured*in vitro* , but the former may only be assessed *in vivo* . Successful COVID-19 vaccines must incorporate rational strategies to avoid *both* ADE of viral infection of cells *in vitroand* formation of immune complexes/immunopathology *in vivo* . All current, reported COVID-19 vaccine candidates incorporate intact viral spike domains, and none are designed to avoid *both* of types of ADE. Although some vaccines, such as Pfizer's BNT162b1, contain only the receptor binding domain (RBD) of the viral spike, prior studies with the closely related SARS virus have established that neutralizing antibodies targeting the RBD exhibit ADE[9].

The justifications for the whole spike vaccine immunogens in the current COVID-19 vaccines currently in clinical trials insinuate an equivalence of this COVID-19 pandemic to past influenza pandemics. This can be reassuring, as effective vaccines for the influenza and H1N1 viruses were rapidly achieved using the traditional recipe for vaccine development. However, autologous immunity following influenza infection is the rule rather than the exception, which is consistent with the success of influenza vaccines in combatting influenza pandemics, like H1N1, where the time frame is too short to allow significant viral antigenic variation. However, immunity following SARS-CoV-2 infection is less well established. Antigenic variation is indeed not the vaccine challenge for the SARS-CoV-2 pandemic, contrary to frequent allusions expressed in both scientific and lay public reports: the 108 sequences of the SARS-CoV-2 spike protein in GenBank (accession date Mar 27, 2020) are 100% identical, and only a single amino acid mutation has been reported worldwide (http://virological.org/t/first-report-of-covid-19-in-scotland/412), and it is not in an antigen location. Instead, the better viral comparator for SARS-CoV-2 is the non-pandemic RSV, with a similarly conformationally metastable, but not particularly antigenically variable, viral spike that has resisted an efficacious vaccine for more than 50 years and precipitated a coronavirus-similar, vaccine-enhanced disease syndrome[10].

Study design issues

Since vaccine-elicited anti-SARS-CoV-2 spike antibodies may themselves be harmful, current vaccine trial endpoints may be incorrectly chosen. The first phase of human testing of current COVID-19 vaccines are designed to be validated, at least partly, on immunogenicity, which is defined as elicitation of high titers of anti-pathogen antibodies by the vaccine. Immunogenicity measured in this way usually ignores the function and efficacy of vaccine-elicited antibodies, and is a low bar for vaccine candidates, which only remains in contention due to distant historical efforts, such as attempts to develop vaccines for encapsulated pathogens like *Neisseria* and *Pneumococcus* . Thus, in the case of COVID-19 disease, vaccine-elicited anti-SARS-CoV-2 may be detrimental or, at least, of uncertain benefit, making their appearance and titer a puzzling choice

of milestone for vaccine advancement. The technological improvements that have been leveraged to produce the current SARS-CoV-2 vaccine candidates have nearly all been platform-based: e.g. lower cost and faster manufacturing of DNA or RNA vaccines, viral vectors, skin inoculation, etc. Accordingly, the question in the current vaccine trial of SARS-CoV-2 spike mRNA of whether the vaccine is immunogenic is a question entirely about the technology platform and not a predictor of efficacy of the vaccine. As for safety, public data on ongoing COVID-19 vaccine trials do not disclose whether antibody-mediated immunopathology is defined as an Adverse Event of Special Interest, and indeed several of the trials, and nearly all the trials outside the US, restrict Adverse Event monitoring to 28 days, which would be too soon to observe worsened COVID-19 disease due to exposure to circulating SARS-CoV-2 viruses (Source: clinicaltrials.gov). Accordingly, some of the current viral candidates will almost certainly pass a Phase I immunogenicity and safety test, even if they have significant delayed ADE or immunopathology liabilities. Similarly, Phase III trials may be incorrectly designed if their primary endpoint is reduction in infections rather than reduction in immunopathologic disease. If vaccine-worsened disease is indeed a relevant phenomenon for COVID-19 vaccines, one could easily imagine a scenario in which infections are reduced but immunopathologic disease incidence is not or is actually higher in vaccinees. Approval of such a vaccine would not be in the public's best interest.

Current data on COVID-19 vaccines show no evidence of ADE of disease. Non-human primate studies of Moderna's mRNA-1273 vaccine showed excellent protection with no detectable immunopathology[11]. Phase 1 trials of several vaccines have not reported any immunopathology in subjects administered the candidate vaccines, however these subjects were unlikely to have encountered circulating virus yet[12]. Nevertheless, all preclinical studies to date have been performed with the Wuhan or closely related strains of the virus, while a mutant D614G virus is now the most prevalent circulating form, and several observations suggest that this alternative form may be antigenically distinct from the Wuhan derived strain, not so much in composition, but in conformation of the viral spike and exposure of neutralization epitopes[13-15]. Similarly, Phase 1 and 2 clinical trials of vaccine candidates have not been designed to capture exposure of subjects to circulating virus after vaccination, which is when ADE/immunopathology is designed to occur. Thus, the absence of ADE evidence in COVID-19 vaccine data so far does not absolve investigators from disclosing the risk of enhanced disease to vaccine trial participants, and it remains a realistic, obvious potential risk to the subjects.

Challenges to informed consent for COVID-19 vaccine studies

Informed consent procedures for vaccine trials commonly include disclosure of very minor risks such as injection site reactions, rare risks from past, *unrelated* vaccines/viruses, such as Guillan-Barre syndrome for swine flu and generic statements about the risk of serious idiosyncratic systemic adverse events and death. Specific risks to research participants derived from biological mechanism are rarely included, often due to ambiguity about their applicability[16]. Given the overwhelming evidence in the extant literature, however, all COVID-19 vaccine trials are unlikely to meet the required threshold of patient comprehension if clear and specific disclosure, in the informed consent, of the risk of worsened COVID-19 clinical course or death from acute lung, blood, cardiac or other tissue injury upon SARS-CoV-2 viral exposure due to vaccine-elicited antibodies is not provided to research subjects. These risks should be clearly and emphatically distinguished in the study informed consent from risks observed *rarely* as well as the more obvious risk of lack of efficacy, which is unrelated to the specific risk of ADE. Based on the extant literature, it should have been obvious to any skilled medical practitioner in 2020 that there is a significant risk to vaccine research subjects that they may experience severe disease once vaccinated, while they might only have experienced a mild, self-limited disease if not vaccinated. The limited benefit of immunogenicity endpoints for investigational COVID-19 vaccines should also, perhaps, be clearly disclosed. The consent should also clearly distinguish the specific risk of worsened COVID-19 disease from generic statements about risk of death and generic risk of lack of efficacy of the vaccine. Given the "laundry list" nature of informed consents, disclosure of the specific risk of worsened COVID-19 disease from vaccination calls for a specific, separate, informed consent form and demonstration of patient comprehension. The alarming rumors of emergency consideration in COVID-19 vaccine trials of unprecedented "viral challenge clinical trial" designs, wherein subjects would be intentionally challenged with live virus after vaccination, call for this level of consent to protect the moral and legal rights

of human subjects recruited to participated in these vaccine trials. While the COVID-19 global health emergency justifies accelerated vaccine trials of candidates with known liabilities, such an acceleration is not inconsistent with additional attention paid to heightened informed consent procedures specific to COVID-19 vaccine risks.

Author Contributions

TC and RV conceived this commentary. TC wrote the manuscript. RV edited and approved the manuscript.

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