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The conundrum of current anti-SARS-CoV-2 vaccines

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has given rise to the urgent need for vaccines and therapeutic interventions to address the spread of the SARS-CoV-2 virus. SARS-CoV-2 vaccines in development, and those being distributed currently, have been designed to induce neutralizing antibodies using the spike protein of the virus as an immunogen. However, the immunological correlates of protection against the virus remain unknown. This raises questions about the efficacy of current vaccination strategies. In addition, safety profiles of several vaccines seem inadequate or have not yet been evaluated under controlled experimentation. Here, evidence from the literature regarding the efforts already made to identify the immunological correlates of protection against SARS-CoV-2 infection are summarized. Furthermore, key biological features of most of the advanced vaccines and considerations regarding their safety and expected efficacy are highlighted.

1. Introduction

By the end of January 2021, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had infected more than 100 million people, causing approximately 2.2 million deaths [1]. Given the nature and severity of coronavirus disease (COVID-19), there is a need to fight the viral spread through behavioral changes and social and medical interventions. Among the latter, widespread efforts have been made to produce vaccines for large-scale administration. All current vaccine strategies have been developed to generate anti-spike protein (S) neutralizing antibodies (Abs). This strategy has been pursued through different technologies via the delivery of messenger RNA (mRNA), adenoviral vectors, recombinant proteins, and inactivated viral particles.

The urgency in tackling the pandemic strongly reduced the time allocated to the three phases typically needed to achieve vaccine licensure. However, unproven technologies have been proposed and pursued to produce vaccines that are currently being distributed. Applied on a global scale, these new strategies could achieve important advancements in vaccine technology. However, in some cases, safety concerns need to be revisited.

Furthermore, two additional aspects must be considered in the overall evaluation of vaccines: efficacy and duration of immune response. The immunological correlates of protection against SARS-CoV-2 infection are still unknown. On the other hand, the restricted observation times did not allow a reliable evaluation of the duration of immune response induced by the current anti-SARS-CoV-2 vaccines.

Here, useful data are summarized from the literature to clarify the course of humoral immunity in SARS-CoV-2-related pathogenesis in humans. On this basis, the expected efficacy and the duration of immune response of diverse vaccines are evaluated. In addition, possible issues concerning the safety profiles of the diverse vaccines are analyzed.

1.1. What is the immunological correlate of protection against SARS-CoV-2 infection?

Most commonly, the term “correlate of protection” refers to a laboratory parameter associated with protection from a clinical disease [2]. When this concept is applied to the immune response against SARS-CoV-2, there are several uncertainties. For instance, data from a detailed immunological study on hundreds of infected patients, extended for up to 8 months after symptoms onset, did not provide definitive conclusions about the mechanisms of protective immunity [3]. On this basis, it has been proposed that a coordinated action of CD4+ T cells, CD8+ T cells, and neutralizing Abs is necessary to control SARS-CoV-2 infection [3,4]. Results from a study on rhesus macaques...
indicated that adequate levels of anti-SARS-CoV-2 immunoglobulin G (IgG) can protect against infection and that cellular immunity contributes to protection in the case of subprotective Ab titers [5].

With regard to the virus-induced humoral response in humans, specific Ab responses were found to be elevated in severely ill patients, but remained moderate-to-low or even undetectable in asymptomatic subjects and patients with mild disease [6–11]. This applied to anti-S protein and anti-receptor-binding domain (RBD) Abs, that is, Abs recognizing the S domain binding to the angiotensin-converting enzyme 2 (ACE-2) cell receptor, and to all Ab classes [12–15]. The highest levels of neutralizing Abs, that is, the anti-S Abs identified for their specific ability to block virus entry in vitro assays, were found in patients with more severe illness [15,16]. Serological time course analysis carried out on hospitalized patients failed to demonstrate a correlation between anti-S Ab levels and patient outcomes [15]. However, many deceased patients developed very high levels of anti-S, anti-RBD, and neutralizing Abs [15,17–19]. In addition, the kinetics of the decay of anti-S, anti-RBD, and neutralizing Abs was strongly correlated [15]. This evidence goes against the hypothesis that the quality, rather than quantity of Ab response, may predict the patient’s outcome.

Taken together, these clinical observations raise serious questions about the correlates of protection against a SARS-CoV-2 infection.

1.2. What is the duration of immune response of anti-S Abs?

The duration of the induced immune response is a critical hallmark of any vaccine. The humoral immune response relies on the production of Abs as well as the generation of memory B cells that can undergo reactivation upon antigen recognition. The duration of the anti-SARS-CoV-2 antibody response was evaluated for a reasonable time in infected patients. Conversely, the observation times following vaccine administration were restricted. Dan and colleagues reported that the half-life (t1/2) of post symptoms onset (PSO) anti-S Abs was 103 days, as calculated in infected patients tested at least at two time points [3]. The half-life of anti-RBD Abs was 69 days, and that of neutralizing Abs was 27 days. In these cases, the decay curves were recognized as extended plateaus. In contrast, the t1/2 of anti-S and anti-RBD IgAs did not exceed 30 days. In this study, the levels of anti-S humoral response appeared variable, with more than 2 logs of difference among infected subjects [3]. In another study, a parallel decay of anti-S, anti-RBD, and neutralizing Abs was reported, starting at one to a few months after symptoms onset, with inpatients developing higher Ab titers than outpatients [15]. This decline was more rapid in asymptomatic and mildly ill patients. In general, data from Ab levels and kinetics of decay appear inconsistent among different investigations [3,12,13,15,20,21].

Ab waning may not necessarily imply unresponsiveness in a subsequent antigen recognition, considering that humoral immunity can be promptly reactivated in the presence of a pool of memory B cells. In the case of SARS-CoV-2 infection, different studies have demonstrated the persistence of circulating virus-specific memory B cells for up to 8 months [3,22–24]. However, the formation of a pool of memory B cells in airway tissues remains uncertain. Lymphocytes residing in the lungs are essentially a self-renewing cell population, and this population is only minimally replenished by circulating cells [25]. Thus, the presence of virus-specific circulating memory B cells would not necessarily mirror adequate levels of immunity in lung tissues, which are the region most involved in SARS-CoV-2 pathogenesis. This may be a critical issue in the case of anti-SARS-CoV-2 vaccines, since the rapid decrease in Ab response in the absence of an effective pool of memory B cells in the lungs may imply the requirement of frequent booster doses.

1.3. Vaccines based on mRNA technology

This is the first time that vaccines based on mRNA technology have been proposed for the human population. These vaccine formulations comprise mRNA molecules where uracil bases are replaced with a pseudouridine analogue [26] and complexed with hydrophobic lipid nanoparticles [27] to allow efficient entry into the cells of the injected host. The lipid nanoparticles are 70–100 nm in diameter and are prepared using an ionizable amino lipid, phospholipids, cholesterol, and a polyethylene glycol (PEG)-ylated lipid [28]. In the case of anti-SARS-CoV-2 vaccines, mRNA codes for a SARS-CoV-2 S protein with two proline mutations that stabilize its prefusion conformation [29] in order to favor the generation of neutralizing Abs. Because of lipid complexing, injected mRNA molecules can access the cytoplasm of host cells, thereby initiating S protein synthesis. The viral protein is assumed to be secreted and recognized by the host immune system as a non-self product that eventually elicits humoral immunity. When the mRNA molecules enter an antigen-presentation cell, peptides derived from the neo-synthesized product may be uploaded to major histocompatibility complex (MHC) class I molecules, thereby initiating the process leading to an antiviral CD8+ T-cell immune response.

A wealth of data supports the conclusion that this strategy leads to a robust humoral response [30–32] associated with apparent protection from severe symptoms [33–35]. To the best of our knowledge, mRNA-based vaccines do not present major safety concerns, besides short-term adverse reactions of limited severity. However, at present, nothing is known about unpredictable, long-term adverse reactions that could have been monitored only by extended phase III clinical trials. In addition, the limited observation times preclude a reliable evaluation regarding the duration of humoral response and need for Ab response reactivation.

1.4. Vaccines based on human adenoviral vectors

The use of adenoviral vectors is considered the “gold standard” in preclinical vaccine experimentation because of the high levels of humoral and cellular immune response against the antigen of interest that these vectors elicit in animals. This technology has been translated into anti-SARS-CoV-2 human vaccines with vectors derived from both human and non-human primate virus strains.

Adenoviruses are non-enveloped, icosahedral viruses approximately 90 nm diameter, with a linear double-stranded DNA genome of 28–40 kilobases, expressing 22–40 genes depending on the virus type [36]. Human adenoviruses have more than 50 serotypes, divided into seven species (A to G). Serotypes 2 and 5 are the most widely studied. Adenoviruses can infect dividing and non-dividing cells, and have a broad tropism.

Adenoviral vectors are generally produced in mammalian cells by recombination between homologous parts of the genome. In classic laboratory protocols, DNA molecules expressing a replication-defective adenoviral backbone and a shuttle vector carrying the gene of interest are co-transfected in mammalian cells, complementing the backbone defectiveness. Sequences of the gene of interest are transferred to the viral backbone through recombination, guided by homologous sequences present in the two DNA molecules. Adenoviral vectors are commonly produced by co-transfection in HEK-293 cells engineered to complement the defectiveness in the viral backbone, most frequently involving deletions in the E1a, E1b, E3, and E4 genes. In more advanced technologies, the homologous recombination step occurs in bacteria [37]. The most popular adenoviral vectors are based on the genomes of serotypes 5 and 26.

Two aspects should be considered when adenoviral vector-based technology is applied to human vaccines: (i) the engineered adenoviral genome is quite large and expresses, besides the gene of interest, several additional proteins including capsid proteins II (hexon), III (penton base), IIIa, IV (fiber), VI, VIII, and IX; core proteins V, VII, and X; and the terminal protein TP, and (ii) adenoviral genomes are prone to recombination, a feature that can have consequences in the case of non-human adenoviral vector-based vaccines.

The injection of adenoviral vector particles implies that a single vaccine administration can generate a widespread immune response
against the structural adenoviral products. The unavoidable vector-specific immunity could be minimized by the use of last-generation, high-capacity adenoviral vectors [38]; however, these have not yet been approved for clinical use.

Adenovirus infection in immune-competent individuals mostly results in mild, self-limiting pathologies. It is quite common in humans, and virus-specific IgGs persist after infection. For instance, 60–80% of a Chinese population had neutralizing Abs against adenovirus serotype 5, and 20–50% had neutralizing Abs against serotype 26 [39]. The data obtained by analyzing a Brazilian population was consistent with the findings of the Chinese population [40]. In another study on individuals from sub-Saharan Africa, 100 % of persons displayed neutralizing Abs against serotype 5, and 21 % against serotype 26 [41].

Despite these premises, anti-SARS-CoV-2 vaccines based on adeno-viral vectors from serotype 5 have been produced and administered [42]. In some instances, the vaccination schedule includes boosting with a vector based on serotype 26 [43], which has the advantage of a lower seroprevalence in humans. In other cases, the vaccination schedule includes two inoculations with a vector from serotype 26 [44]. Vector neutralization, ultimately inhibiting the anti-S immune response, is expected to occur in all subjects already experiencing natural infection with serotypes 5 and/or 26. In case of uninfected subjects, anti-vector immunity takes place after the first immunization, which severely curtails the efficacy of vaccine boosts. Furthermore, the anti-vector immunity is also expected to heavily affect possible re-boostering, which is to be applied after the decay of the immune response induced by the first vaccination cycle.

The CD8⁺ T-cell response against the diverse adenoviral proteins that natural infection and vaccine administration can elicit, is also a hurdle. In this regard, adenovirus-specific CD8⁺ T lymphocytes have been proven to be widespread, polyfunctional, and cross-reactive against antigens from different human serotypes, as well as from vectors derived from non-human primates [45].

1.5. Vaccines based on non-human adenoviral vectors

In an effort to elude the neutralization effects of pre-existing immunity, vaccines based on vectors from non-human primate adenoviruses have been produced and are currently being administered [46–49]. The underlying technology is essentially the same as that used to produce vaccines based on vectors from human adenoviruses. After the first inoculation, anti-vector immunity would strongly decrease the immunogenicity of these vaccine preparations. Most importantly, the delivery of non-human adenovirus-based vectors puts vaccine recipients who were previously infected with human adenoviruses at a risk of generating new and unpredictable chimeric virus species. In fact, severely pathogenic virus species may arise as a result of recombination events. Recombination is quite frequent within adenovirus genomes, as largely documented by data obtained by sequencing genomes from people co-infected with different human adenovirus types [50–52]. In vaccinated individuals, a non-human viral vector may enter a single cell that is already infected with a human adenovirus. Considering the very high sequence homology between human and non-human primate adenoviruses (> 95 %), intracellular recombination events are likely to occur. Even if at present only theoretical, the likelihood that a similar, potentially catastrophic event may occur is expected to increase with the increase in the number of vaccinations.

1.6. Vaccines based on inactivated viruses and recombinant proteins

Anti-SARS-CoV-2 vaccines based on the association of recombinant trimeric S protein with adjuvants [53], as well as the whole inactivated virus [54], have also been designed and produced. These approaches resemble “traditional” vaccine strategies already applied to fight other infectious agents, and hence in principle possess high safety profiles. However, issues with Ab efficacy and the duration of immune response are expected to mirror those already described for the humoral responses elicited through less conventional vaccine strategies.

2. Conclusions

The major unresolved issue in current anti-SARS-CoV-2 vaccine strategies is that the immunological correlates of protection against the virus in humans remain unknown. Results from several clinical observations are consistent with the idea that the levels of anti-S Abs do not correlate with patient outcome, and this evidence may have consequences for predicting vaccine efficacy. It is conceivable that quality (e.g., affinity, avidity, and specificity) rather than quantity of Abs produced will be critical for virus blockade. More accurate laboratory analyses are required to validate this hypothesis since, at present, the patient outcome appears to be independent of the relative amounts of anti-RBD and neutralizing Abs produced.

A potential obstacle in the development of a SARS-CoV-2 vaccine is the risk of triggering Ab-dependent enhancement (ADE) of virus infection and/or immunopathology, as has already been documented for SARS-CoV [55–57] and has been recently suggested for SARS-CoV-2 [58–60]. The lack of ADE-related events during the current mass vaccination tentatively excludes the possibility that some vaccines might worsen the disease rather than prevent it, as seen with the Dengvaxia tetravalent yellow fever-dengue Ab-generating vaccine [61].

Vaccine strategies employing adenoviral vectors are controversial in terms of efficacy and safety. Further, when not already present, as in the case of vectors based on non-human adenoviruses, the induction of neutralizing anti-vector immunity seems unavoidable, as also described in recent clinical trial reports although in sparse and hidden ways [42, 44]. An additional inhibitory mechanism is represented by vector-specific CD8⁺ T-cell immunity. When adenoviral vectors enter professional and semi-professional antigen-presenting cells, peptides from viral proteins can associate with MHC class I molecules, thereby eliciting pools of CD8⁺ T lymphocytes that recognize, attack, and destroy cells expressing the products of adenoviral vectors. These events would strongly limit the effectiveness of vaccine boosts.

The most alarming perspective pertains to the use of non-human adenoviral vectors. It is widely accepted that new and aggressive epidemics arose from the passage and adaption of viruses from animals to humans. This was hypothesized, among others, for HIV, avian and swine influenza viruses, and, lastly, SARS-CoV-2. In the case of vaccinations with non-human adenoviral vectors, natural barriers can be overcome by delivering a non-human viral genome directly into cells. DNA recombination between different adenovirus species may occur when the target cells are already infected with a human adenovirus. Since DNA recombination events are based on the recognition of stretches of identical sequences, and there is high sequence homology between human and non-human primate adenoviruses (> 95 %), the emergence of recombinant adenoviruses from vaccinated individuals is, although rare, a possible event. The positive selection of even a single new pathogenic adenovirus species would have unpredictable and unger-nnbarable consequences globally.

It is conceivable that protection against SARS-CoV-2 infection would be the result of the coordinated action of humoral and cellular immunity. Consequently, besides the induction of neutralizing Abs, additional antiviral preventive strategies should be pursued. Several experimental and clinical studies prove the beneficial effect of virus-specific CD8⁺ T-cell immunity. T cells provide therapeutic benefits by directly inducing lysis of virus-infected cells and shaping the immune response through the release of cytokines critical for suppressing viral infections. CD8⁺ T-cell responses against respiratory viral infections have been shown to be as important as humoral responses [62–64]. Robust T-cell responses against S, membrane (M), nucleocapsid (N), and ORF1ab proteins have been described in COVID-19 convalescent patients [65,66]. The T-cell response present in asymptomatic and mildly ill infected patients is absent in severely ill patients [67–69]. Notably, CD8⁺ T-cell responses
Novel virus variants harboring mutations in S protein and particularly in the RBD, the target of most neutralizing Abs, are emerging worldwide. Current vaccines were based on the S protein sequence from the virus isolated early in the epidemic in Wuhan. Many groups have published data on vaccine cross-neutralization. Results from two recent studies based on different in vitro neutralization assays concluded that current mRNA-based vaccines cross-neutralize both P.1 (Brazil variant) and B.1.351 (South African variant) poorly [71, 72]. Due to the widespread diffusion of the virus, the rapid emergence of mutations is not surprising. Redesigning vaccines based on new sequences may result in an element of selective pressure in the case of large-scale vaccinations. Conversely, a strategy for a universal vaccine including a component that induces effective CD8+ T-cell immunity could break such a potential vicious circle.

Although a strong CD8+ T-cell response should be a component of any vaccine regimen for SARS-CoV-2, no reliable vaccine technology for the induction of cell immunity has been validated for humans to date. In this regard, adenoviral vectors produced reproducible positive results in preclinical settings in terms of induction of CD8+ T-cell immunity in a wide range of applications. However, results from trials with anti-SARS-CoV-2 human vaccines appeared modest [39] and, in some cases, elusive [35].

In conclusion, the extraordinary rapidity of producing diverse anti-SARS-CoV-2 vaccine options has caused several questions about their efficacy, duration of immune response, and safety. Intensive basic and preclinical research is needed to define pathogenesis, immunopathogenesis, and correlates of protection against SARS-CoV-2 infection. This is the only way to achieve safe and effective preventive and therapeutic interventions.

Declaration of Competing Interest
The authors report no declarations of interest.

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