THE PUBLISHING HOUSE
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ANTI-SARS-CoV-2 IMMUNE RESPONSE AND PREVENTION OF COVID-19 PANDEMIC BY VACCINATION

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Accepted February 22, 2021

Coronaviruses are large, enveloped, single-stranded, positive polarity RNA viruses, infecting both humans and a wide range of domestic and wildlife animal species. Although coronaviruses are common etiological agents of an important fraction of human acute respiratory infections, three types (i.e. SARS-CoV-1, MERS and SARS-CoV-2) proved to be highly pathogenic, causing severe clinical infections and high mortality rate and having epidemic and pandemic potential. The activation of both cellular (infected cells elimintion) and humoral (free virions neutralisation) immune response are required to eradicate SARS-Cov-2 associated infections. In the context of the evolving COVID-19 pandemic, many strategies and technological platforms have been approached for obtaining an efficient vaccine. The purpose of this review is to present the main types of anti-SARS-CoV-2 available vaccines, with their main advantages and disadvantages, highlighting both safety and efficacy issues.

Keywords: coronavirus, SARS-CoV-2, molecular vaccines, S spike, RBD, mRNA, adenovirus vector, cellular immunity, neutralizing antibodies.

INTRODUCTION

Coronaviruses are large, enveloped, single-stranded RNA viruses, with one of the largest of RNA positive polarity genome of all riboviruses, infecting both humans and a wide range of domestic and wildlife animal species. Coronavirides are classified into two subfamilies: *Letovirinae* and *Orthocoronavirinae*. Out the four genera of the *Orthocoronavirinae* (*α*-, *β*-, *γ*- and *δ*-*Coronavirus*), the first two infect only mammals, while the last two primarily infect birds, but have also been isolated from pigs. Until now, seven types of human coronaviruses are responsible of 5–10% from the total of acute respiratory infections (common cold) and the healthy carriers of coronaviruses represent about 2% of the human population. Three types of highly pathogenic coronaviruses, *i.e.* severe acute respiratory syndrome coronavirus (SARS-CoV)-1, MERS and SARS-CoV-2 have epidemic and pandemic potential, causing severe clinical infections and high mortality rate [1]. In 2002-2004, SARS-CoV-1 caused 8098 infections, with 774 deaths in 29 countries, after which it disappeared. In 2012, MERS, using the dipeptide-peptidase-4 (DPP4) to internalize in the host cells emerged in Saudi Arabia with sporadic outbreaks, responsible, by January 2020, for 2519 cases, with 866 deaths (35% mortality). Until now, SARS-CoV-2 associated disease – 2019 (COVID-19) has spread in only one year in more than 180 countries or regions and affected over 27 million people, with a fatality rate of 3.3%[2].

Both SAR-CoV-1 and SAR-CoV-2 viruses use the same receptor, ACE2 (angiotensin converting enzyme-2), for entering the animal and human cells through the S-spikes, this allowing them to overcame species barriers and infect humans[3-5]. Another unifying feature favoring the interspecific

propagation is the use of tissue protease – furin, which cleaves the glycoprotein S, in S1 and S2 fragments, the last one bridging the viral peplos and the ACE2 membrane receptor, mediating the fusion of the two structures, allowing the progression of infectious cycle, i.e. the passage of the nucleocapsid into the cytoplasm [5,6]. The 3 'end of the RNA genome encodes the synthesis of four structural (glyco)proteins, which are important both for virulence, but also for the development of diagnosis tools: S (spikes), M (matrix), E (envelope), all included in peplos and N (genomic RNA-associated nucleoprotein) [3,7,8]. The protein trimer S, but also the RBD (receptor binding domain) sequence of S1 (composed of 6 amino acid residues) are attractive targets for the production of the anti-COVID-19 vaccines[9]. The three glycoproteins embedded in peplos confer distinct serological specificity to different groups of the Coronaviridae family, thus the infection with a certain serotype does not offer cross-protection against infection with other serotypes of the same coronavirus [10].

Coronaviruses have a marked tendency for genomic variability, by mutation and recombination, due to the functional peculiarities of RNA-dependent RNA polymerase. Genome sequencing of 220 viral strains highlighted the high incidence of mutations especially in the genomic region of replicase. These mutations triger the viral evolution, allowing its adaptation to new hosts, avoidance of defense mechanisms or resistance to therapeutic agents[11]. Mutations in the genes encoding for peplos glycoproteins can generate new antigenic variants, but only a limited variation in the viral pathogenic potential[10].

ANTI-SARS-CoV-2 IMMUNE RESPONSE

The activation of both humoral (free virions neutralisation) and cellular response (infected cells elimintion) are required to eradicate a viral infection. The first actors are the resident macrophages. They secrete interleukin (IL)-1, which attracts neutrophils and monocytes at the infection primary site [10]. The prompt antiviral response of phagocytes eliminates the virus before it multiplies in the cells of the oropharyngeal epithelium and the infection remains in the contamination stage without clinical signs. The early synthesis of IFN-I has also an important role in the elimination of viral particles, before infecting and multiplying in the epithelial cells, by inducing an antiviral state in ther non-infected cells. It has been shown that the early administration of IFN-I ameliorates the pathological lesions caused by an exacerbated inflammatory response [12]. In exhange, de delayed IFN-I productions stimulates the massive influx of neutrophils and macrophages in the lung tissue, leading to the necrosis of alveolar pneumocytes and macrophages, alveolar vascular exudate, respiratory failure and eventually, to fatal outcome [13-16]. The functional inefficiency of phagocytes causes the infection to progress to the intracellular phase of viral multiplication, with the activation of a Th_1 response. Th_1 lymphocytes recognize the viral Ag exposed on the surface of infected cells and activate the specific cellular immune response. Its activation provides long-term protective memory because it is oriented against highly higly-preserved viral proteins. Clinically, the stage of viral multiplication which surpased the cellular immunity corresponds to acute infection, with the release of viral Ag into the extracellular space. Subsequently, after the release of the progeny virions, the immune response switches to a Th_2 type, stimulating the antibody mediated humoral response. The synthesis of IgM is very important in primary infection with a highly virulent virus.

Severe manifestations of the infection are the result of activating the inflammatory process. Infected epithelial cells stimulate inflammation in the lung tissue, with a major influx of neutrophils and macrophages. In the viremic phase, the inflammatory reaction becomes systemic, with the involvement of the digestive tract, kidney, liver, heart muscle, which endangers life. The excessive stimulation of the inflammatory process is characterized by a “cytokine storms”, with neutrophils, eosinophils, macrophages, dendritic cells migrating into the infected tissues and releasing a cascade of proinflammatory Ils. IL-1[17], induce the synthesis of IL-2, -4, -6, -7, -10, -12, -13, of monocytes- and respectivley macrophages-attractant proteins (MCP and MIP) etc.[18]. IL-6 induces the hepatic synthesis of acute phase proteins, chemokines and C-lectins (mannose-binding lectin-MBL). The number of TCD_8 lymphocytes and NK cells decreases by about 50%, but the remaining ones secrete perforin and granzymes, with lesional effect on the host cells[13,14]. The complement activation, through the C3a and C5a anaphylatoxins release, amplifies the pathological process of the acute respiratory syndrome. C5a inhibits neutrophils apoptotic death, amplifying the inflammatory process[19] and

induces the synthesis of IL-8 which stimulates thrombogenesis and multi-organ lesions (lungs, heart, liver, kidneys) with local hemorrhagic necrosis characterize, explaining the high levels of troponin and D-dimers resulting from the process of degradation of fibrin clot under the influence of plasmin, seen in critically ill patients[14,20].

SARS-CoV 2 infection induces severe immune system dysfunctions: spleen and lymph node atrophy, functional depletion of T lymphocytes, manifested by decreased number of Th and Ts lymphocytes in secondary lymphoid organs, especially in critically ill patients. The percentage of naive (uncommitted) Th lymphocytes increases, and that of memory Th lymphocytes and Treg lymphocytes decreases[14,21].

SARS-CoV-2 VACCINES

Vaccination is one of the most effective medical interventions and has significantly contributed to reducing the morbidity and mortality of infectious diseases. The administration of a vaccine is based on a well-defined strategy, aiming to eradicate, eliminate or limit an infectious process. Vaccines can be prepared pathogenic bacterial or viral strains whose virulence has been attenuated by cultivation under special environmental conditions, or from chemically pathogens (*e.g.*, with formaldehyde, ethylene oxide, thiomersal, or b- propriolactone) [10]. In terms of complexity, vaccines may be whole unit vaccines, containing all the antigenic components of the infectious agent, or subunit vaccines, prepared from fractionated antigenic components, which must induce the synthesis of specific antibodies, inactivating the infectivity of the infectious agent. The route of vaccine administration influences the intensity and efficiency of the immune response. The optimal routes of administration of inactivated vaccines, to which an adjuvant is added, intended to increase the persistence of the vaccine, are intramuscular and subcutaneous. The subunit, molecular antigens stimulate the synthesis of IgG and IgM, whose serum titer reaches high values. In SARS-CoV-2 infection, the protective effect of serum antibodies is installed in a later phase, after the infection descends to the depth of the bronchial tree. To stop the infection early, protection should be manifested primarily at the entry gate of the viru, *i.e.*, the epithelium of the respiratory and digestive tract[22,23].

In the midst of a pandemic with SARS-CoV-2, which surprised the world's population without immune protection and appropriate vaccine production capacity, specialists are looking for the different variants of a protective vaccine. Given the similarity of SARS-CoV-1, SARS-CoV-2 and MERS and the probability of a cross-immune response, an important focus is the research for a broad-spectrum coronavirus vaccine [24].

The conceptual and technological platforms for vaccine production are diverse: inactivated vaccines, attenuated vaccines and vaccines obtained through recombination, each of them probably more suitable for different age or population groups. The choice of one or another production method is conditioned by various factors (technological, sanitary, economic) [9]. Clinical trials for licensing a vaccine must go through 4 phases: phase I – to determine safety and dose, with administration to young volunteers; phase II – evaluation of immune response stimulation; phase III – evaluation of efficiency, after administration to a large number of people (thousands), of all ages; phase IV – approval that guarantees safety and long-term effects. Under the current pandemic, this desideratum will be validated or not after an interval considered acceptable.

1. ATTENUATED WHOLE UNIT VACCINES

In the context of the evolving pandemic, the strategy of obtaining an attenuated vaccine remains an alternative perspective. One of the methods consists in the selection of mutant strains of SARS-CoV 2 with attenuated virulence, by successive passages on semipermissive cellular substrates. Another methods is based on the observation that most respiratory viral infections, including SARS-CoV-2, are inapparent or mild. Inapparent ones do not stimulate the immune response and do not produce immunological memory. However, some of the infected individuals may have maintained a residual state of immunity after a previous infection with a common cold coronavirus, which would suggest the prospect of producing a vaccine following the model of E. Jenner's smallpox vaccine: a coronavirus strains which is infectious for animals, but harmless to humans, provided the biochemical and structural homology of the S spikes of the vaccine virus, with the S spikes of SARS-CoV-2.

The attenuated coronavirus vaccine will contain infectious virions which, after subcutaneous or intramuscular inoculation, will be transported by blood and lymph and will multiply in the same tissues as the wild virus, without producing pathological manifestations, except at most in a mild form, ensuring robust immunization. The main benefits of such a vaccine are that it stimulates both cellular and humoral specific immune response, essential for sterilizing the outbreak of viral infection and is cheaper to fabricate. The disadvantages are that: it is instable and therefore, can be stored only for maximum four days at 4^{o}C before administration; the risk of spontaneous reversal mutation to te a sufficiently virulent form to cause infection in those vaccinated and in their contacts; administration to people with immunodeficiencies and to the elderly can reproduce the pathological picture of the natural infection; the strategy requires a large amount of virus, very unlikely to be achievable in the short term.

The attenuation of SARS-CoV-1 was achieved by deletion of the E protein, activator of the inflamasome (which exacerbates the inflammation of the lung) and of the NS16 protein to avoid IFN I activation. In the absence of NS14, the fidelity of genomic RNA replication decreases significantly[17].

2. INACTIVATED WHOLE UNIT VACCINES

Inactivated vaccines contain virions which, after inactivating chemical treatment, do not initiate the multiplication cycle in the permissive substrate. The crude viral preparation stages are the cultivation of SARS-CoV-2 virus in the permissive cell substrate – VERO line cells – followed by subsequent inactivation with formaldehyde, ethylene oxide, thiomersal, or b-propriolactone. It was produced by Sinovac, the Beijing Biological Institute and the Wuhan Homologous Institute [25].

The benefits of inactivated vaccin are that it eliminates the risk of reversion mutation to virulent virus; it can be administered to immunodeficient persons and to those undergoing immunosuppressive therapy; it does not introduce into the community the infectious virus that can eventually spread uncontrollably in the population; it has a minimal risk of infection. Rarely, inactivated preparations may contain residual infectious virus, which may resist inactivation treatment, or which may result from contamination with another virus.

As for the disadvantages, treatment with a chemical agent can cancel the immunogenicity of some viral proteins, essential for the stimulation of protective immune response; it can induce only a low level of local immunity (respiratory and intestinal), so that SARS-CoV-2 can multiply in these sites, in vaccinated people; it does not stimulate the cellular specific immunity (mediated by Tc lymphocytes), which has a decisive role in eliminating virus-infected cells and in resisting infections with a wide range of viruses; the protective titer of IgG has a limited duration and requires periodic vaccination; the production costs are high; it can cause a pulmonary influx of eosinophils, generating pathological lesions, in patients with incipient allergic conditions.

The development of a classic vaccine with attenuated or inactivated virus requires a long period for licensing, which for Ebola was 5 years.

3. SUBUNIT VACCINES

The initial preparation of subunit vaccines was based on the purification of the entire protein trimer S of SARS-CoV-1 that induced a neutralizing humoral immune response in the preclinical phase. However, the S protein separation requires appropriate technology, involving treatment steps with chemical agents, with the risk of denaturation and loss of native conformation and immunogenic potential.

Subsequently, the subunit vaccine preparation was based on the 6 amino acid sequence of the RBD of protein S[26,27]. Repetitive anti-RBD antibodies neutralized the virus infectivity for a period of 6 months[7].

Although subunit vaccines stimulate the immune response less intensely compared to conventional, whole unit vaccines, the urgent need for a SARS-CoV-2 vaccine has stimulated the diversification of different platforms for the production of molecular anti-SARS-CoV-2 vaccines, most of them based on the cloning or inserting the gene that encodes the S protein in plasmid or viral vectors, such as: a) cloning and expression of the gene for protein S in a cellular system and purification of the protein; b) insertion of S cDNA into the plasmid; c) obtaing the S protein mRNA; d) obtaining a recombinant S protein homologous to SARS-CoV-2 native S protein; e) using a viral vector as carrier of the S gene; f) using virus-like particles (VLPs), expressing self-assembled SARS-CoV-2 surface structural proteins (S, E, M, N) that reproduce the structure of the peplos, having a conformation

similar to that of native proteins, but do not contain any genetic material VLP containing highly repetitive Ag have been already used for the anti-papilloma and anti-HBV vaccine[28]. These different platforms represent a huge step in the progress of molecular medicine and biotechnology[29] and are in different stages of evaluation to obtain production licensing.

MRNA vaccines produced by Pfizer / BioNTech and Moderna

The mRNA encoding the integral S protein or RBD contains modified nucleotides allowing its translation into immunogenic proteins and is encapsulated in lipid nanoparticles (LNP), to increase the stability against cytosolic RNA-ses. LNPs are composed of cationic lipids, i.e. cholesterol to stabilize NPL; phospholipids that facilitate the passage into cells and release from the endosome; PEGylated lipids to decrease nonspecific interaction [30].

Pfizer / BioNTech has created 4 vaccines: BNT162b1, BNT162b2, BNT162a1 and BNT162c2: 2b1 encodes the RBD trimer of protein S; 2b2 encodes the entire S protein sequence; 2a1 – mRNA harbors pseudouridine instead of uridine; 2c2-a self-amplifying RNA. BNT162b2 has been shown that it disadvantageously induces antibodies without neutralizing activity of the infectious virus, but stimulates the antibody dependent enhancement (ADE) reaction [31]. In Moderna mRNA vaccine, the amino acids 986 and 987 are replaced with Proline so that they stabilize the S protein in the prefusion conformation, to prevent stimulation of IFN synthesis.

The advantages of the mRNA vaccine are the following: they do not have the risk of genotoxic effects (they do not interact with cellular DNA); in the preclinical phase studies they stimulated both humoral and cellular immune response; the became available in a very short time they. The main disadvantages are that they can activate the synthesis of IFN which inhibits the translation and accelerate mRNA degradation, being also associated with the activation of the inflammatory cascade.

Protein vaccines

Viral proteins are synthesized by SARS-CoV-2 infected cells and released in soluble form into the culture medium. Separation methods must retain their native conformation so as not to alter their immunogenic properties. The principle of production is to identify the immunodominant region of the vaccine candidate (*e.g.*, the RBD region of the S protein), followed by peptide production. Otherwise, the peptide will not stimulate a strong immune response. The Novavax vaccine contains the entire S-protein sequence, genetically modified for better structural stability in the prefusion state [30].

DNA vaccines using plasmid vectors

The DNA vaccine consists of inserting the S-protein cDNA into a bacterial plasmid vector, introduced into the cells by electroporation. The S antigen is synthesized in the cell in its native conformation. The advantages are that this type of vaccine is easy to produce, requires only simple storage conditions because plasmid DNA, unlike chromosomal DNA, renatures rapidly, while maintaining biological activity and no adverse effects were recorded in clinical trials.

The disadvantages are: the low immunogenicity, because the plasmid does not spread and does not replicate in the body; the interaction of the plasmid vector with the nucleus and the risk of the integration of the plasmid in the cellular DNA, with oncogenes activation; synthesis of anti-DNA antibodies can initiate an autoimmune conflict and lead to autoimmune diseases, such as lupus; may induce a chronic inflammatory reaction due to prolonged stimulation of humoral immune response.

DNA vaccines using viral vectors

Viral vectors are recombinant viruses containing in their genome the S-protein cDNA. Chimpanzee adenovirus (ChAdOx1) is used as a viral vector in case of AstraZeneca vaccine. The viral vector is inoculated intramuscularly and is translocated into the nucleus. A mammalian promoter [32] has been attached to the vector structure that is activated and transcribes mRNA from the cDNA gene. The cDNA is transcribed by RNA-polimerase II into mRNA, which will be translated into S protein.

The advantage is that the inoculation of the attenuated virus is equivalent to the natural infectious process: it stimulates both cellular and humoral immunity. TCD_4 lymphocyte activation has indirect antiviral effects, by producing the antiviral IFNγ and activating the CD_8 cytototoxic lymphocytes. TCD_4 memory lymphocytes persist after decreasing the antibodies titer [33].

The disadvantages consist in the fact that the vector interacts with the nucleus, creating, at least hypothetically, the risk of interaction with chromosomal genes and production of subsequent

neoplasia; also, previous anti-adenoviral immunity could cancel the immune response.

SAFETY AND EFFICACY OF VACCINES

Efficacy and safety are the two parameters that evaluate the usefulness of any vaccine. Reports state that both types of molecular vaccines, DNA and mRNA-based, stimulate the two compartments of the immune system [32,34], with the titer of circulating and neutralizing antibodies showing significant values [35]. Persistently infected cells are lysed by TCD8 lymphocytes. As a result, the major goal of any SARS-CoV-2 vaccine should be the stimulation of cellular immunity, which is essential for the lysis of persistently infected cells[36]. This will prevent the infection recurrence which is caused by the acceleration of the multiplication rate of the persistent virus [37,38]. In this regard, the BCG vaccine is a strong immunomodulator and stimulant of the cellular immunity, and could be an effective way to protect against SARS-CoV-2 infection.

The SARS CoV-1 experience shows that antibodies specific for protein S persist for about 2–3 years after infection and a similar immunological profile is expected for SARS-CoV-2[39]. The duration of efficacy of SARS-CoV-2 vaccines cannot be assessed yet, however, until now, most reports on the seroprevalence of anti-SARS-CoV-2 antibodies suggest that the duration of the protective effect lasts for several months and that the immunological memory of B lymphocytes after SARS-CoV-1 infection seems to be short[40]. SARS-CoV 2 undergoes mutations with a frequency almost as high as the influenza A virus, with an average of 1.60 / 103 nucleotides / year. The accumulation of high-rate mutations within a few months could generate new antigenic variants. An example is represented by the English viral strain that underwent 24 point mutations throughout the genome [36].

The ability of molecular vaccines to stimulate the IgA synthesis in the lymphoid structures associated with the respiratory and digestive tracts at the SARS-CoV-2 entry site in the human body is questionable. IgA is the only class of antibodies that, in dimeric form, can be transferred as sIgA to the surface of the epithelia and provide protection against respiratory viruses, including SARS-CoV 2. The titer of IgG and serum IgA does not significantly influence the concentration of sIgA at the respiratory and digestive tract mucosa level, as s IgA is synthesized, in the largest proportion, at the level of local lymphoid structures: *i.e.*, the Waldeyer lymphoid ring and, respectively, the Peyer's patches. Administration by nasal instillation of the adenovirus vector vaccine of the S-protein cDNA would, in all probability, be more effective for the protection of the respiratory, but also digestive mucosa, the circulation of the lymphocytes in homologous structures. The lymph nodes are the essential structural sites for the activation of immune response and for the maturation of the anibodies affinity, as well as for the antibodies class switching. Therefore, for optimal stimulation of the immune response, the vaccine must be conditioned to be lymphatically drained into the lymph nodes [30].

The mRNA molecules can activate the cascade of innate and acquired immunity activating events. The mRNA is endocytosed, released into the cytosol and translated by the protein synthesis cellular apparatus. Prior to translation, mRNA can bind to PRR (pattern recognition receptors – TLR3, TLR7, and TLR8) in endosomes or the cytosol, and RIG-I (retinoic acid inducible genes) and MDA5 (melanoma differentiation protein 5) recognize the RNA double strands in the cytosol. The result is the activation of proinflammatory mechanisms, including IFN-I mediated inflammation and NF-κB nuclear translocation[41]. On the other hand, IFN-I amplifies the antiviral immune response: it stimulates the maturation of dendritic cells, of TCD8 and the release of IL-12 and IL-23. Excessive synthesis of IFN-I can lead to disruption of immune tolerance and to autoimmune reactions.

The risk of activating the inflammatory reaction and generating autoimmune conflicts is higher in young women, most prone to autoimmune diseases, auto-inflammatory reactions, due to overexpression of chromosome X-linked genes, which dominate the antiviral response. On the other hand, estrogens stimulate immune reactivity.

The potential risk of the ADE phenomenon is also invoked. After the decrease of the titer, the remaining non-neutralizing antobodies can stimulate the infectious process through the ADE phenomenon, demonstrated for Denga virus, HIV and for cats coronavirus, facilitating the antobody mediated engulfment of viral particles coated with non-neutralizing serum IgG in the host cells and the initiation of the infectious process [39,42]. However, this would imply that the respective viruses could multiply in cells bearing the receptors for the Fc region of the antibodies molecules (*i.e.,* professional phagocytes or innate

immunity lymphoid cells) [43]. The intrinsic (iADE) could however lead to the activation of phagocytes that could release their content of cytoplasmic granules: degradative enzymes and proinflammatory IL, which could cause the cytokines storm, amplifying the intensity of the pathological process. Another side effect that could occur after vaccination is the hypersensitivity reaction to the preservatives found in the inactivated vaccine (*e.g.*, formalin) [39].

CONCLUSIONS

Although seven types of coronaviruses are known since long time, being common etiological agents involved in an important fraction of human acute respiratory infections, three types (*i.e.* SARS-CoV-1, MERS and SARS-CoV-2) proved to be highly pathogenic, causing severe clinical infections and high mortality rate and having epidemic and pandemic potential. The activation of both cellular (infected cells elimintion) and humoral (free virions neutralisation) immune response are required to eradicate SARS-Cov-2 associated infectious disease-19 (COVID-19). In the context of the evolving pandemic, many strategies have been approached for obtaining an efficient vaccine. The whole unit vaccines can be either attenuated (obtained by applying specific cultivation methods or by using a coronavirus strain which is infectious for animals, but harmless to humans) or inactivated (by chemical treatment). The whole unit vaccine would stimulate both cellular and humoral specific immune response, but, in the case of attenuated ones, they could raise problems related to stability and have a risk of spontaneous reversal mutation to the virulent form, while, in the case of inactivated ones, the chemical agent can cancel the immunogenicity of some viral proteins. Moreover, the development of a classic vaccine with attenuated or inactivated virus requires a long period for licensing. The initial preparation of subunit vaccines was based on the purification of viral S protein or on the synthesis of the 6 amino acid sequence of the receptor binding domain (RBD) of protein S. Then, the production of molecular anti-SARS-CoV-2 vaccines was based on the S protein gene cloning or insertion in plasmid or viral vectors. The already available vaccines are the mRNA-based vaccines encoding the integral S protein or RBD from Pfizer and Moderna, the Novavax vaccine containing the entire S-protein sequence, DNA based vaccines using viral (chimpanzee adenovirus) vectors (AstraZeneca). Regarding the safety, besides mild local or general side-effects, the mRNA vaccines can stimulate an intensive proinflammatory cascade, hypersensitivity reactions, disruption of immune tolerance and as well as stimulation of the infection cycle by the antibody dependent enhancement reaction could occur.

Reports state that both DNA and mRNA-based vaccines stimulate the two compartments of the immune system. The major goal of any SARS-CoV-2 vaccine should be the stimulation of cellular immunity, which is essential for the lysis of persistently infected cell, preventing the infection recurrence and assuring a long term immunological memory. The efficiency of SARS-CoV-2 vaccine is threatened by the viral mutations that could generate new antigenic variants. Also, the vaccine should stimulate the production of sIgA synthesis to assure mucosal protection and prevent the initiation of the infectious process, and, in this regard, the administration by nasal instillation would be desirable. Also, for optimal stimulation of the immune response, the vaccine must be conditioned to be lymphatically drained into the lymph nodes.

Acknowledgements. This research was funded by the grant PN-III-P2-2.1-SOL-2020-0090-Contract 13Sol/15.06.2020, project "Advanced techniques for early SARS-CoV2 detection".

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