



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Editorial



New generation of vaccines and convalescent plasma therapy for management of CoV-2: Perspectives from the UK and potential deployment in the current global pandemic

Coronavirus COVID-19 (official nomenclature SARS-CoV-2), has, since March 2020 when the WHO announced its pandemic nature, created major challenges in the world, causing a public health crises with severe economic consequences. A crucial element of this highly contagious virus is its capability to propagate exponentially into susceptible hosts, often causing severe inflammatory thrombotic microcirculatory events leading to multiorgan dysfunction and emergency hospitalisations, causing chaos in healthcare systems.

To rescue the population demands that an armamentarium of preventative and therapeutic modalities be implemented based on the lessons learned by utilisation of personal protective equipment and implementation of efficient testing and contact tracing. Preventative and therapeutic measures include the use of some available automated tools in big data or pattern and procedural analyses and the introduction of convalescent plasma therapy. While imperfect, we have had some partial success by use of some clinical strategies such as anti-viral, anti-inflammatory, and anti-thrombotic drugs recruited, on the basis of laboratory results which have helped to resolve some challenging issues.

Recently, innovative mobile plasmapheresis technologies with in-line affinity column absorption and therapeutic blood purification systems have proven to be useful in reducing the toxicological aspects of convalescent plasma therapy and the hyper concentrated neutralising antibody used to create passive immunity. Moreover, some novel developments, with fast track approaches to producing and distributing some candidate vaccines, with an efficacy above 70 % that still remains an enormous task to surmount in view of the demand, and we are waiting, with hope, the stringent regulatory safety report on newer bioproducts for intramuscular injection. Studies are also in progress for an inhaled dry powder version of a vaccine as are more targeted approaches for localised drug delivery strategies such as red cell extracellular microvesicles [EV].

Introducing vaccinotherapy during this pandemic to decrease the rate of infection through creation of herd immunity, is directed at reducing the disease to a manageable level in hospitals. Many countries have developed approaches to produce and evaluate the efficacy and safety of numerous types of vaccines for their national supply or for other countries. These include the 3 well known front runners, the vaccines from Pfizer and Moderna which are based on mRNA technology of the spike proteins of the virus and the UK Oxford / AstraZeneca vaccine and some others that follow preplanned dose regimens for the initiation of an immune response followed by a second dose after 3–4 weeks to enhance efficacy. These have shown acceptable levels of neutralising antibody comparable to that which is found in convalescent plasma.

Based on a literature survey of some characteristic profiles of the current candidate vaccines that are under development it is clear that a balanced humoral and Th1-directed cellular immune response, the two essential pillars for protection of vaccine-candidates are achievable to a high degree of satisfaction, with no major untoward clinical outcomes.

These include the nucleic acid vaccines, inactivated virus vaccines, live attenuated vaccines, protein or peptide subunit preparations and viral-vectored vaccines. In principle, the development of a vaccine could be obstructed if the virus later evades immunity to the spike glycoprotein used to construct the vaccine.

The characteristic profiles of the main seven candidate vaccines either waiting regulatory permission or having obtained permission to be used are briefly described below:

a] The Oxford University (Oxford, UK) and AstraZeneca, a chimpanzee adenovirus-vectored vaccine, encoding the spike glycoprotein of SARS-CoV-2, shows the induction of humoral responses characterized by anti-spike glycoprotein IgG and neutralising antibodies, and IFN γ T-cell responses in most recipients (18–55 years of age) after the first dose of vaccine, even at half of the standard dose with a better response and an additional increase in humoral immune outcome after a second dose. The humoral immune response in vaccine recipients was similar to that observed in convalescent plasma from patients who had recovered from CoV-2. This vaccine requires refrigeration not the ultra low storage which could be problematic for use in low-income countries. It has been considered in the UK as the “World Vaccine” having no commercial aspect and costs about £3;

b]. Moderna and the National Institutes of Health have jointly developed an mRNA-based vaccine (mRNA-1273) consisting of a sequence-optimised mRNA encoding the spike glycoprotein encapsulated in lipid nanoparticles with two doses (10 μ g or 100 μ g), given 4 weeks apart inducing both spike glycoprotein binding and virus-neutralising antibody responses. These humoral immune responses, seen in recipients aged 18–55 and over, are similar to results observed in convalescent plasma from patients who had recovered from COVID-19. Vaccine recipients also developed cellular responses, mainly biased towards CD4⁺ Th1 cells. CD8⁺ T-cell responses were marginal, except for those in recipients of two vaccinations with a higher dose (100 μ g).

One potential issue for vaccine deployment is that a storage temperature of –20 °C is required and the cost is higher at £28;

c]. Pfizer and BioNTech have developed a mRNA-based COVID-19 vaccine which is also a lipid nanoparticle-formulated, nucleoside-modified mRNA. It elicited RBD-binding IgG and neutralising antibody. Participants, aged 18–85 years, were randomly assigned to receive two intramuscular doses [of either 10 μ g, 30 μ g, or 100 μ g] separated by 21

<https://doi.org/10.1016/j.transci.2021.103051>

Available online 11 January 2021

1473-0502/© 2021 Published by Elsevier Ltd.

days, and the results were equal or better than those observed in a human convalescent serum panel. The results of the cellular and humoral immune and T-cell responses of another selected candidate vaccine of this series were excellent too. These types of vaccines require storage at -80°C , which is logistically problematic and the vaccine cost is about £15. It is important to highlight that the UK government ensured, well in advance, a large supply of this vaccine and such a product has already arrived from Belgium in a stored frozen state and was used on Tuesday 8th December (V-Day) in England and Scotland in front line workers and aged groups in home care units. This is the first in European-transatlantic countries.

d]. The Janssen Pharmaceutical Companies of Johnson & Johnson have initiated a phase 3 trial in participants aged 18 years and older of their replication-defective Ad26.COVS vaccine, which expresses full-length spike glycoprotein. The results have shown that a single immunisation with this adenovirus serotype 26-vectored vaccine (1.0×10^{11} viral particles by the intramuscular route without adjuvant), induces strong neutralising antibody responses and provides protection against a SARS-CoV-2 challenge in an animal study. This candidate vaccine, which requires storage at $2-8^{\circ}\text{C}$, is now being tested in those aged 18–55 and ≥ 65 years) in the USA, Belgium and the UK but the company has not yet publicly released details of the vaccine's safety profile, efficacy or cost;

e]. The Gamaleya National Research Centre for Epidemiology and Microbiology (Russian Federation) have published the results of two phase 1/2 clinical trials of their COVID-19 vaccine consisting of recombinant adenovirus serotype 26 (rAd26) vector and recombinant adenovirus serotype 5 (rAd5) vector, both carrying the gene for the SARS-CoV-2 spike glycoprotein (rAd26-S and rAd5-S). These candidate vaccines (1.0×10^{11} viral particles per vaccine dose) were tested in 76 healthy individuals aged 18–60 years who were given either a single dose of the rAd5-S vaccine in phase 1, a single dose of the rAd26-S vaccine in phase 1, or both rAd5-S and rAd26-S in phase 2. The first study examined frozen vaccine formulations (0.5 mL per dose; stored at -18°C), and the second study examined lyophilised formulations (1.0 mL per dose, stored at $2-8^{\circ}\text{C}$) Neutralising antibody titres equal to or greater than the titres observed in convalescent plasma from patients who had recovered from COVID-19 were seen, moreover, the CD4^{+} and CD8^{+} cell immune responses peaked at day 28 after vaccination. Interestingly, while more than 70,000 people have already been vaccinated with success, president Putin is offering mass vaccination with 3 types of vaccines that are already available [-70 storage; -15 and dry version] for military, doctors teachers etc. This is a real breakthrough, even compared with the UK government success.

f]. China-based CanSino Biologics has developed a recombinant adenovirus serotype 5-vectored COVID-19 vaccine that expresses the SARS-CoV-2 full-length spike glycoprotein from the Wuhan-Hu-1 virus strain, and is given at 3 doses to those age 18–60. The phase 3 trial includes 40,000 participants age 18 years and older and is underway in Pakistan and China. Information on storage conditions has not yet been released for this vaccine but, conceptually, storage conditions are likely to be similar to those of other vaccines based on adenovirus vectors and might involve either refrigeration or storage at -20°C .

g]. SinovacBiotech(CoronaVac) is a chemically inactivated, whole-virus preparation administered in a two-dose regimen (on day 0 and day 28) and was granted emergency use authorization by Chinese authorities in July 2020, before the initiation of phase 3 studies. Nearly 90 % of company employees were immunized with two intramuscular injections, either $3 \mu\text{g}$ per 0.5 mL or $6 \mu\text{g}$ per 0.5 mL of the trial vaccine, or placebo, either on day 0 and day 14, or on day 0 and day 28. The vaccine elicited anti-RBD antibodies in 97.4 % of those receiving the vaccine at 0 and 28 days. Importantly, neutralising antibody responses were significantly higher in younger adults (aged 18–39 years) than in older adults (aged 40–59 years), and stronger responses were noted in participants given the second dose on day 28 than in those given the second dose on day 14. No published data exist in regard to measures of cellular

immune responses to this vaccine. A phase 3 trial has been launched in Brazil and Indonesia, with the trial in Brazil aiming to enroll 9000 health-care personnel.

h]. Sinopharm has developed and are testing two inactivated whole-virus, alum-adjuvanted vaccines.

The neutralising antibody titres were generally similar in concentration to those produced by other COVID-19 vaccines and were higher in the group vaccinated on days 0 and 21. In addition, lymphocyte subsets and cytokines were measured by flow cytometry and did not show changes across study groups, suggesting that cellular immune responses might not have been generated. This vaccine is planned to be used in participants in the United Arab Emirates, Bahrain, Peru, Morocco, Argentina, and Jordan and given to health-care personnel and groups at high risk of becoming infected.

i]. The second vaccine candidate being tested by Sinopharm was developed by the Beijing Institute of Biological Products. A phase 3 trial is taking place in the United Arab Emirates which granted emergency use of the vaccine in health-care providers. Sinopharm has reportedly administered these experimental vaccines to hundreds of thousands of people under an emergency use condition approved by the Chinese Government. Looking at the status of future research developments, some concerns are expressed in the context of the potential antibody-dependent enhancement [ADE] mechanisms associated with various new generations of CoV-2 vaccines. ADE mechanisms involve the virus uptake into Fc gamma receptor IIa (FcγRIIa), expressing phagocytic cells which could cause enhanced inflammation and immunopathology by excessive antibody Fc-mediated effector function or immune complex formation. ADE is a potential hurdle for antibody-based vaccines carrying the risk of exacerbating COVID-19 severity. [ADE in viral disease: Source: <https://www.nature.com/articles/s41564-020-00789-5>]

To sum up, although different groups have successively achieved the key milestones of CoV-2 vaccines, little attention has been given to the mechanism of ADE involvement potentially causing the delayed auto-immune reactivity previously reported to be present in convalescent plasma used as the standard to achieve the objective of obtaining the reliable levels of antibodies and the duration of ADE effectiveness remains to be studied in different populations with so called poor and good responders. Accordingly, there are still some matters that need to be sorted out:

1] Antibody response is an important component of protective immunity during SARS-CoV-2 infection. In antibody-dependent enhancement, heterotypic (non-neutralising) antibodies might have the potential to facilitate viral entry into cells through interaction with Fc receptors or complement. Even in the absence of active viral replication in immune cells, this process might lead to the activation of macrophages, monocytes, and B cells, and IL-6, $\text{TNF}\alpha$, and IL-10 production which need to be considered.

2] These are concerns regarding the potential for antibody-dependent enhancement in individuals who are infected with SARS-CoV-2 after vaccination with differing types of COVID-19 candidate vaccines, as the potential risk of antibody-dependent enhancement mediated by Fc receptors could be increased with mutations in the SARS-CoV-2 spike glycoprotein, which could weaken the primary host antibody response;

3] Cases of antibody-dependent enhancement induced by vaccines have been reported in some cases after the use of formalin-inactivated vaccines against respiratory syncytial virus and measles, and a vaccine against dengue virus where monocyte, macrophage, and B-cell infections might occur in numerous tissues subsequent to unstable virus-antibody complexes, leading to extensive apoptosis of immune cells and the production of inflammatory cytokines;

4] As to whether the mechanism of enhancement might involve the interaction of antibodies with conformational epitopes in the ACE2-binding domain is unknown and the study of antibody-dependent infection of human macrophages by SARS-CoV-1 suggests the potential role of anti-spike glycoprotein IgG in the infection of immune cells

and downstream signaling pathways of FcγRII receptors which trigger the antibody-dependent enhancement. Some additional study in this direction is warranted, although previous SARS-CoV-2 exposure could have a role in non-human primate produced antibody-mediated protection with no sign of acute lung injury and immunopathology;

5] Antibody-dependent enhancement poses a theoretical obstacle to vaccine development and is being carefully evaluated. The extent to which pre-existing antibodies to SARS-CoV-2 (and, potentially, to SARS-CoV-1) might contribute to antibody-dependent enhancement and disease severity remains in question, however, no evidence of antibody-dependent enhancement has been found in animal models or in humans in phase 3 clinical trials.

Much remains to be learned regarding coronavirus immunity in general and SARS-CoV-2 immunity in particular, including the protective immunity induced by vaccines and the maintenance of immunity against this virus. Furthermore, multiple vaccine types will probably be needed across different populations (e.g., immune-immature infants, children, pregnant women, immunocompromised individuals, and immunosenescent individuals of age ≥ 65 years). In addition to the adaptive immune response, there are some data suggesting that trained

innate immunity might also have a role in protection against COVID-19. It is, therefore, crucial that research focuses on understanding the genetic drivers of infection and vaccine-induced humoral and cellular immunity to SARS-CoV-2, defining detailed targets of humoral and cellular immune responses at the epitope level, characterizing the B-cell receptor and T-cell receptor repertoire elicited by infection or vaccination, and establishing the long-term durability and maintenance of protective immunity after infection or vaccination.

A safe regulatory pathway leading to licensing must be defined for use of these vaccines in children, pregnant women, immunocompromised people, and nursing home residents. Some have called for further shortening of the vaccine development process through the use of controlled human challenge models the UK is considering initiating such trials in early 2021.

Jerard Seghatchian

International Consultancy in Innovative Manufacturing and Quality/Safety of Blood-Derived Bioproducts, London, England, UK
E-mail address: jseghatchian@btopenworld.com.