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Immunotherapy for COVID-19: Evolving treatment of viral infection and associated adverse immunological reactions

Jeffrey S. Putter [1]

Medical Biomechanics Inc., San Diego County, CA, United States

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ABSTRACT

This review on COVID-19 immunotherapy enables a comparative analysis of the short-list of currently approved major vaccines. These include the Pfizer and Moderna first mRNA vaccines under FDA purview and the Oxford/AstraZeneca simian adenovirus-vectored vaccine (under UK-MHPRA guidance), all produced in record time, being safe and effective. The Pfizer and Moderna double dose vaccines have the clear edge in treatment efficacy, being in the 90% range compared to AstraZeneca in the average 70%. However, the AZ double dose vaccine has significant advantages with respect to lower cost and stability in storage.

We enumerate several potential advances in the technology of the manufacturers: **(1)** combination vaccines such as testing AstraZeneca's product with a component of the Russian's Sputnik V to achieve durable immunity; **(2)** the potential for single dose vaccines coming on-line, and with Johnson & Johnson/Janssen; and **(3)** the need for refined thermotolerant formulations obviating the need for cold storage.

As an adjunct to vaccinotherapy, affinity adsorption column technology is another facet recruited in the processing of corona convalescent plasma/cryosupernatant to concentrate neutralizing antibodies against the virus. Clinical trials, to date, of infected patients have been indeterminate as to whether plasmapheresis-based products are effective or not. This is due to the failure to standardize the composition of the plasma derived component, ambiguous clinical indications for use in human subjects, and inconsistent timing of administration in the course of the infection. Known T-cell lymphopenia, which is attendant to progressive viral infection and immune driven inflammation, may be a quantitative surrogate biological marker as to when to start treatment. This is not only for initiating plasmapheresis-based therapeutics but also the judicious selection of ancillary pharmaceuticals, ie. monoclonal antibodies, recombinant proteins and anti-viral drugs.

1. Introduction

Coronavirus COVID-19 (official nomenclature of SARS-CoV-2) has created a public health emergency with serious economic consequences. A crucial element of the virus is its' capability to propagate easily through susceptible hosts via the respiratory route, being extremely contagious and causing severe acute respiratory syndrome (SARS) [1]. SARS-CoV-2 (2019 to present, originating in the city Wuhan, east China), is more infectious than SARS-CoV-1 (2001–2004, originating in Guangdong Province, south China) with the former transmitting itself exponentially world-wide [2].

The enhanced degree of infectivity of SARS CoV-2 appears to be mediated by the virus's S-spike protein and CoV-2′s high affinity binding to the angiotensin converting enzyme (ACE-2) and neuropilin-1 (NLP1) host cell receptors [2–4]. The severity of the contagion, concomitant multiorgan dysfunction and deranged physiology are responsible for rising hospitalizations that have stressed the healthcare system.

Despite quarantine measures, a new variant, B.1.1.7 lineage (a.k.a. 20B/501Y.V1) Variant of Concern (VOC) 202012/01, recently appeared in the capital and southeast of England. This variant has surfaced in several other countries including the United States and Canada. Preliminary epidemiological evidence suggests the new UK variant is more transmissible but there is no existing evidence of greater virulence or capacity to evade vaccine induced immunity [5]. The emergence of the UK variant coupled with the previous surge in infectious cases have triggered extensive travel bans to France, Germany, Belgium, Netherlands, Ireland and even Scotland and worries of associated economic consequences.

The coronavirus SARS-CoV-2 epitomizes the perfect example of a storm, a nightmare pandemic scenario which requires rescue plans for

E-mail address: Jputter@LTSP.com.
[1] Medical Biomechanics Inc., 100 E. San Marcos Blvd., Suite 400, San Marcos-North San Diego County, CA 92069 USA.

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the population. An armamentarium of anti-viral, anti-inflammatory, and anti-thrombotic drugs is being recruited to the problem: research in plasmapheresis-based exchange technologies to decrease inflammatory mediators; in-line affinity column adsorption to prepare neutralizing antibody concentrate to the virus; recent novel developments in vaccines with reported efficacies in the range 62–95%, ie. the mRNA and simian adenovirus-vectored vaccines; and partial success with the implementation of personal protective equipment and physical distancing.

2. Status of vaccine therapy

With respect to vaccine R&D, the current focus is on developing efficient manufacturing and distribution (DMDP) on a mass scale. Multiple newly designed and validated vaccines have reached their final safety and efficacy evaluations for the prevention of disease. Nearly 11 vaccine candidates, so far, are in various stages of development and approval to achieve the critical herd immunity at global levels of 70% and stem the pandemic. This means intensive financial investment into the vaccination infrastructure. The intent is to optimize distribution, education of the public and, importantly, emphasize that vaccines are not a panacea, requiring continued vigilance with respect to all personal protection measures.

Three different types of production technologies are being employed among many candidate vaccines, several recently accelerated into phase III safety/efficacy trials and gaining medical agency approval. These vaccines have harnessed multiple technologies: **(i)** mRNA technology using a copy of the spike protein of the coronavirus that binds with ACE-2 and neuropilin on the cell membranes; **(ii)** the conventional viral vector technologies; and **(iii)** recombinant protein methods [6].

2.1. mRNA constituted vaccines

These include the mRNA vaccine candidate BNT 162b2 manufactured jointly by Pfizer (Kalamazoo, MI USA) and BioNTech (Mainz, GE) (reported preliminary 95% efficacy and FDA emergency use authorization (EUA) December 2020, est. £14.34/dose). The pairing of the two companies synergistically harnesses BioNTech's vaccine technology with Pfizer's worldwide development, regulatory, vaccine manufacturing and distribution capabilities; Moderna's mRNA vaccine, Cambridge, MA, USA (reported preliminary 94.5% efficacy and FDA/EUA approved December 2020, est. £11.03–18.39/dose). In the United States, an emergency use authorization is **not** an approved licensed drug by the FDA but allowed limited use for the period of the emergency.

Another forward-looking approach is to develop a single efficacious dose vaccine, having cost and product distribution advantages. The single dose mRNA Johnson & Johnson/Janssen candidate capitalizes on this approach, their phase III trials just launched in the United Kingdom, United States and European communities with the results expected by April of 2021. The European Commission has pre-approved procurement of up to 400 million doses of this vaccine.

The methodology of the approved mRNA-based vaccines Pfizer/BioNTech and Moderna Covid-19 are unique compared to conventional vaccines. Conventional vaccines use attenuated or dead forms of the germ, which have been previously grown in eggs or cell cultures necessitating a complex, time intensive process to manufacture the vaccine. In juxtaposition, the novel mRNA vaccines incorporate a **non-viral** blueprint mRNA that encodes instructions specific for synthesis of a non-virulent spike protein within the human cell. The mRNA uptake by the human cell is facilitated by a lipid nanoparticle vehicle carrier (LNP) [7,8]. At vaccination, the synthetic spike protein derived by genetic engineering is then presented on the external membrane of the cell triggering a host immune response to include neutralizing antibodies, CD4 helper cells, cytotoxic CD8 cells and memory B cells. Later, upon true infection with coronavirus, its native spike protein rapidly engenders the host's own protective innate immune response, which had been previously primed by the vaccine. It should be emphasized that the mRNA does not enter the nucleus of the cell, does not change the cell's DNA profile, and, conceptually, is degraded after translation of its' instructions to a small molecule [7].

2.2. Adenovirus-vectored vaccines

The Oxford University/AstraZeneca's simian adenovirus-vectored AZD1222 vaccine has come on-line (efficacy reported in the 62–92% range, UK-Medicines and Healthcare Products Regulatory Agency UK-MHPRA approved December 2020, one of the cheapest, est. £1.47−2.94/ dose). AZD1222 is based on the chimpanzee adenovirus-vectored platform (ChAdOx1/AZD1222) encoding the spike glycoprotein of SARS-CoV-2. The implementation of the AZD1222 *COV002* (UK) vaccine trial mandated two full administered standard doses ($5{\cdot}0 \times 10^{10}$ viral particles) within 28 days. Because of comprehensive quality controls instituted by the manufacturer, it was discovered that a half dose priming injection (2.2×10^{10} viral particles) followed by a full booster dose had been given in a smaller treatment arm. Administration of this low dose was related to differences determined in the accuracy of two different quantitative assays. The assays included spectrophotometry being less accurate than qPCR, the latter confirming a half dose of 2.2×10^{10} viral particles and subsequently adjusted to a full standard dose of $5{\cdot}0 \times 10^{10}$ viral particles [9]. For indeterminate reasons, the incidental lowering of the priming dose associated with this smaller data set had a higher clinical efficacy in the 90% range compared to the average 70% of the larger trial.

A larger phase 3 trial of the AZD1222 vaccine involving 30,000 adults (20 000 vaccine recipients and 10 000 controls) began in August 2020, in multiple worldwide locations. Because the geriatric age group is especially prone to death because of SARS and immunosenescence, AstraZeneca has been expanding their vaccine study to elucidate treatment efficacy and measuring neutralizing antibody levels (NAB) in seniors. Overall, side-effects have been minor; AZD1222 triggers the induction of humoral responses, characterized by anti-spike glycoprotein IgG NABs, IFNγ T-cell responses in most recipients after the first dose of vaccine [10,11].

2.3. Vaccine stability, dosing and timing of inoculations

As guided by the manufacturer's instructions, the FDA package inserts, the Pfizer double doses for administration should be separated by 21 days and the Moderna by 28 days. Regarding the approved use of the Pfizer and Moderna vaccines, both in the USA and UK, the FDA has clear warnings about untested deviations in protocols intended to expand the pool of vaccine recipients. The FDA pointedly states that any possible changes pose a potential significant health risk to the public. Questionable deviations include significant delays in the administration of booster doses up to 90 days, using half rather than full doses, mixing different vaccine doses of disparate manufacturers or even skipping the booster doses. Such deviations lend to legitimate questions for future study in clinical trials but as the FDA warns, are contrary to the accepted science, safety and efficacy data of the recent phase 1,2,3 clinical trials in evidence [12].

The UK government has ordered 100 million doses of AZD1222. It is advantageous that AZD1222 requires only standard refrigeration at a lower level 2–8 degrees C. This contrasts with less stable mRNA vaccines that need to be frozen and kept at cold -20 degrees C for Moderna and even colder -80 degrees C for the Pfizer vaccine.

2.4. Combination vaccines

There is an innovative clinical trial program in progress to test the safety and boost immunogenicity of two combined adenoviral-vectored vaccines. These are the Oxford/AstraZeneca's AZD1222 (**simian** adenoviral-vectored) and Russian Gamaleya Research Institute's

Sputnik V (**human** Ad26 adenoviral-vectored) vaccines [13]. Treatment efficacy of the Russian vaccine alone yields 90%.

2.5. Neglected populations for vaccine research

While teenagers are at lower risk for morbidity and mortality of coronavirus, they are potentially carriers of disease and transmission to high-risk individuals including the elderly. Ongoing vaccine research should not neglect this population, some studies already in Arabic countries, are with the Chinese vaccines for use in adolescents >=age 12.

To date, vaccine trials have neglected pregnant women even though they have a heightened risk of mortality from COVID-19. Given this elevated risk, the manufacturers are currently examining pathways to be inclusive of pregnant women in vaccination programs. This includes reviewing data on women that unknowingly became pregnant during the period of vaccination and surveillance for any adverse pregnancy events. Guidelines for vaccination in pregnancy have been issued by the American College of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine and the Centers for Disease Control. The intent is to weigh risk versus benefits on an individualized basis and to encourage practitioners to frequently review the guidelines for updates. [14].

2.6. Logistical issues of vaccine roll-out

The importance of the development of multiple source vaccines is to satisfy an enormous demand internationally and to avoid overreliance upon a single manufacturer for DMDP. There is an urgent need to educate newer personnel to inject the vaccine and preparatory work is advanced in the United Kingdom and the United States with, the latter's Operation Warp Speed. Recruitment and training of the fire engine staff throughout the UK has begun in anticipation of efficient roll-out of approved vaccines. The UK-MHPRA has a focus on the safety of the Pfizer and Moderna mRNA platform vaccines and the AstraZeneca adenovirus-vectored platform vaccine. The UK-MRHA has a mandate to conduct real time rolling reviews of clinical data to fast track these pharmaceuticals.

Despite the encouraging projections, many unresolved logistical issues remain:

- The ultracold storage of the first mRNA vaccine (Pfizer) wherein refrigeration resources are scare in rural areas. This obstacle is partly overcome in the Moderna vaccine by stabilizing the mRNA which can be kept two weeks in cold, standard freezer temperatures. Given the logistical issues of cold storage, there is ongoing research for improved thermotolerant vaccines in a lyophilized form [15].
- Prioritization of who receives the vaccination; the aged who are most vulnerable, the senior care homes and frontline medical and ancillary support staff.
- The challenge of executing large scale DMDP rapidly. Clearly the infrastructural requirements and distribution to the right places are enormous tasks to accomplish even for well advanced countries.
- Vaccine R&D should follow the best practices, with the applied three **Rs**, being ***R**obust, **R**eliable and **R**eproducible, achieving break through milestone vaccines in less than one year, ready to be implemented with confidence.
- Education to ensure a sufficient proportion of the population is vaccinated to achieve herd immunity and be willing to do so. There is a limited confidence by disadvantaged populations in novel innovative products of vaccine development, including the mRNA vaccines.
- Education to ensure patient acceptance of immunization despite minor transient post-vaccination side-effects.
- The double injection protocols, common to all current vaccines, including the Russian & Chinese types, underscore the importance of investigating the longer-term effects of booster doses of a vaccine given at the 28-day or if delayed, 90-day interval and prolonging the duration of effectiveness in the circulation.
- The importance of the regulatory pillar, the T-reg cells that have a major role in clearing up NAB binding to virus as part of innate immunity [16].

Clinically, it is imperative to evaluate the efficacy of the vaccine regarding the prevention of infection and transmission of the virus, the durability of the response, the recommended interval for re-vaccination, ie. bi-monthly for the first two doses and then probably annually; and if required, to modulate the native vaccine for accrued mutations in the virus structure. Despite the high efficacy reported for the most promising candidate vaccines, exceeding 90%, patients that still become infected could receive convalescent plasma hyperconcentrate replete with neutralizing antibodies to boost their immune response [17].

2.7. Antibody neutralization assay

Regarding the evaluation of live coronavirus in research and clinical settings, it is necessary that all laboratory operations should be handled with care under bioassay level 3 conditions (BSL-3). All the parameters of any antigen or antibody assays should be validated to ensure optimal performance of the reagents by ensuring their stability and determining the sensitivity and specificity of the given tests. The antibody neutralization assay, NAB, is currently used as a standard evaluation procedure of the potency of SARS CoV-2 related vaccinotherapy and also measures the effects of CCP passive immunization [18]. The rapid turnaround time of CoV-2 testing is of relevance in view of the requirement for real time targeted age-related monitoring and testing followed by contact tracing as proposed by the WHO to decrease the community infection rates.

3. Convalescent plasma therapy

As no specific vaccine against CoV-2 with an acceptable safety and efficacy record had been validated against until December 2020 (Pfizer and Moderna and Oxford/AstraZeneca approvals), the use of CoV-2 convalescent plasma (CCP) had gained interest. Passive immunotherapy has been achieved in patients by plasma exchange and the results followed by many clinical investigators internationally but not without controversy. The problem has been the uncontrolled use of CCP given the variability of the products and selection of patients and timing of administration [19,31].

Affinity adsorption column technology can be utilized for the preparation of the immunoglobulin hyperconcentrate [1,20,31]. A component of neutralizing antibodies can be selected from a pool of convalescent plasma (P-NAB) to supplement CCP. This would include optimizing the albumin concentration to countervail the problem of hypoalbuminemia known to occur in seriously ill CoV-2 patients [21]. The longer term goal is to compare various existing CCP products for quality, their record of safety and efficacy and to standardize bioproduct composition, achieving higher levels of CoV-2 NAB in a selected balanced pool of plasma components. Only when these component formulations are standardized is it practicable to conduct well-controlled clinical trials as to product efficacy.

The pathogenesis of systemic inflammation, which surfaces with severe respiratory viral infections, has been reviewed in the context of treatment [22]. Diverse inflammatory mediators consequent to coronavirus infection include disturbances in cytokines, chemokines, and activated complement factors [23]. Abnormalities in clotting factors consequent to excess inflammation perturb the balance of coagulation, either causing impaired hemostasis or excessive thrombosis. Therefore, when collecting CCP from recovering patients of infection, it should not be assumed that the convalescent plasma is ideal for reinfusion purposes without additional processing. Best practices of manufacturing should

consider affinity adsorption column technology to remove the inflammatory driven mediators such as IL6 and; prepare a hyperconcentrate to boost pooled P-NAB resuspended in pooled CCP, and optimise albumin concentrations for infusion purposes and also institute pathogen reduction methodologies to eliminate any residual virus.

The presence of coronavirus neutralizing antibodies is transient and may last for only several months in some cases. Novel bioproducts such as so-called pooled P-NAB hyperconcentrate re-suspended in a cryosupernatant may be advantageous to reboost immunity. One concern is the possibility that pooled-CCP contains some autoantibodies and the effects of such antibodies would potentially counteract the benefits of administering the convalescent plasma [24]. Logically, this is another reason to monitor the levels of CCP-NAB and not to be cavalier about the quality of the convalescent plasma. The above practices are consistent with the concept of personalised precision transfusion, using the best available bioproducts.

4. T-cell lymphodepletion and SARS-CoV-2 infections

Analysis of published data are reported to address a relationship between T cell lymphopenia and the outcome of coronavirus infections, both SARS-CoV-1 and CoV-2 [25,26]. These outcomes have been stratified in various ways to measure cumulative [CD4 + CD8] counts: (1) mild to moderate v. severe disease; (2) survivors v. non-survivors; (3) non-severe v. severe cases; and (4) infected patients v. healthy controls. There are several preliminary conclusions. First, the severity of T-cell depletion correlates with a worse patient outcome for SARS. Secondly, the degree of lymphopenia appears to associate with a cytokine driven hyperinflammatory cascade triggered by coronaviruses. Third, quantitative T-cell lymphodepletion may be a surrogate marker of hyperinflammation and has a potential role to identify the timing of when resource intensive clinical treatments should be applied. Also, recognition of elevated regulatory T-cells (Tregs) as an important T-cell subset to modulate immune responses which may lower the risk of respiratory viral infections in the elderly [16]

5. Monoclonal antibody, recombinant protein and anti-viral drug therapies

The onset of SARS becomes critical in a smaller percentage of patients (estimated 1.4% infection mortality rate) who are innately susceptible to an intense cytokine/chemokine inflammatory response; and with multiple risk factors [27]. The reaction is driven by the virus in the lungs causing massive pulmonary edema and requiring mechanical support by ventilator or even extracorporeal membrane oxygenation. Given the large number of infections in the population encompassed by SARS CoV-2, this percentage of patients with intense inflammation, although small, translates into a major stressor on the limited availability of hospital medical ICU beds and intensivists. Therapeutically, a miscellany of monoclonal antibodies, recombinant protein and antiviral drugs are being tried to attenuate the adverse effects of the hyperinflammatory cascade. These include both tocilizumab, a monoclonal antibody and inhibitor of the interleukin-6 receptor and the recombinant protein anakinra, an interleukin-1 receptor antagonist of the cytokine inflammatory cascade. Remdesivir is an anti-viral prodrug, an adenosine nucleotide inhibitor of the SARS-CoV-2 RNA dependent RNA polymerase (RdRp) essential for viral replication. The drug has shown modest therapeutic effects, shortening the average duration of hospitalisation by four days [28].

6. Extracorporeal immunosorbent devices

To attenuate the host inflammatory factors of SARS, future R&D should progress with specialised immunosorbent devices incorporated into extracorporeal circuits for hemopurification. One such product of potential utility is biocompatible porous polymer adsorbent microbeads [29]. Manufacturers should responsibly ensure such hemopurification devices are secured in the most effective standardised way under strict GMP regulatory adherence.

7. Concluding remarks

As of 10 January 2021, 22:17 GMT, 1,941,757 people have died from the coronavirus COVID-19 outbreak, all from a miniscule RNA virus 0.125 um in diameter. The virus has truly challenged mankind, which despite our ingenuity, the infections and deaths are continuing to rise exponentially in the colder months, facilitated by cohabitation and travel. Despite these rising numbers, we should be sanguine about the prospects for a better future. The Calvary has arrived with the ongoing mass distribution of multiple vaccines and warmer weather only several months away. With encouragement, we should be cautiously optimistic about the longer-term actions of the public for responsibly enhancing the use of personal protective equipment, physical distancing and hygienic practices. Add to this the targeted use of pharmaceuticals and plasmapheresis technologies to mitigate infections and prevent deaths. SARS-CoV-2 is only an awakening with numerous forewarnings, ie. SARS-CoV-1, MERS, Ebola, H1N1 Swine Influensa and seasonal influensa (WHO estimated yearly global mortality of 290,000–650,000 deaths from respiratory causes alone) [30]. Yet we should not to underestimate our resourcefulness. With advancing developmental technologies [31], we should improve in the future.

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