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Short Communication

Revisiting Some of The Unresolved Challenges Associated with Delayed Autoimmune Reactivity and Activation of Inflammatory Process and some Innovative Measures for Safer Alternative Booster Therapies in Targeted Cov-2 Variants Infections: Where We Might Need to be going as the Imposed Restriction in the UK is Coming to End!

Jerard Seghatchian*

International Consultancy in Innovative Manufacturing and Quality/ Safety of Blood, UK

***Corresponding author**

Jerard Seghatchian, International Consultancy in Innovative Manufacturing and Quality/ Safety of Blood – derived bioproducts. London, England, UK, Email: jseghatchian@btopenworld.com

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Abstract

Ever since March 2020, when WHO announced the COVID-19 pandemic, the world has been facing some unsurmountable healthcare and economical crises, due to imposed ever changing nature of CoV-2 variants. Several newer strategies including the use of some anti-inflammatory, anti-viral drug therapy and the use of convalescent plasma were tried internationally to deliver Cov-2 neutralising antibody [CCP-NAB] from recovered patients, by mobile plasma exchange therapy [PET] with the partial success. In parallel in order to reduce the rate of infection down to manageable levels attempts were made to achieving herd immunity, with some validated vaccines, an insurmountable challenge in views of enormous percentage of vaccines hesitancy and strong anti vaccine lobby and the vaccine efficiency not being 100%, there would always 5 to 30% non- responders depending on vaccines' types, even after double jabs of vaccination. Moreover there will be large number asymptomatic individuals that would propagate exponentially the rate of infection, as we are witnessing with the current beta and delta fast spreading variant targeting younger populations, even when doubly vaccinated. Moreover considerable donor/recipient variabilities in the immunological and hematological responses to infectivity exist hence some holistic approach is needed to minimize potential toxicity of vaccine in certain population and eliminated prior to reinfusion of CCP and to provide an answer to the most intriguing questions - is the dynamics of variability's observed early inflammatory-thrombotic patterns to infection and the delayed autoimmune antibody responses, are associated with the high affinity binding of viral spike proteins to ACE2 on the endothelium of cell surface, facilitating viral entry to cell machinery for the infection progression ?.

In the current invited viewpoint commentary after a brief revisit of the scale of above unresolved challenges, some planned progression in provision of a purer, cleaner and new types of NAB –hyperconcentrates obtainable from various sources for emergency delivery of polyclonal NAB against all variants for emergency booster therapeutic purpose, fit for clinical trials are explored with the objective of helping to convert these challenges to opportunity with perseverance, while in the UK restriction is coming to end and we must learn how to coexist with the ever changing nature of the CoV-2 variants.

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INTRODUCTION

SARS-CoV-2, apart from the health and economical chaos, drastically changed most aspects of people lives, works, and how to interact, hence the need for better understanding of dynamics its interaction with our physiological defence mechanisms embodying the infection and vaccine inducing numerous immunological and hematological abnormalities became crucial. Some of these challenging unresolved issues are highlighted below with the objective of finding some remedial actions:

The dynamic of Covid-19 infections inducing immunological abnormalities

It is well established that CoV-2 infection strains do create some unexpected critical illness in some patients, often with an exacerbated delayed immune and inflammatory responses and cytokine storm, often with fatal consequences. Surprisingly these complications do occur, when the immune response system is already initiated but the total viral load is relatively low [1]. Moreover the age -related antibody serological response tends to be much higher in patients with severe disease complications, where the use artificial intelligence and machine learning tools have proven to be instrumental in big data, patterns and procedural analyses, and in developments some innovative preventative and therapeutic modalities that we cannot do without, [2-6].

T Evidence is accumulating that he entry receptor for CoV-2 cell infection is through its high affinity binding to ACE-2, a major component of acute respiratory distress syndrome [ARDS], which opposes the effect of ACE [1]. Moreover ACE-2 is involved in the pathogenesis, liver and lung fibrosis, hypertension, type II diabetes, obesity, reduction of blood volume and in the regulation of the intracellular Na/K balance, all being amongst the characteristic profile of Cov-2 patients. Interestingly recombinant ACE-2 is already a candidate drug for treating patients with ARDS, accordingly viral interference with respiratory system considered to be a major mechanism for pathogenicity and explain the increased rate of complications in some predisposed patients such as: diabetes type II; obesity; hypertension and many others respiratory diseases.

Evidence is also exist that the high affinity viral S1 subunit binding to ACE2 can induce some structural changes that facilitate both cellular entry and a secondary autoimmune response targeted to ACE2 itself, which can extend to the various organs with a high density of exposed cell surface ACE2 [as it is the case, in lungs, liver, heart, small intestine, pancreas, brain, skin], some of the most frequent illness injury sites [1]. Such an immune response could remain in some survivor patients as autoimmune, even when the viral materials are completely eliminated. Therefore exploring the activity states; the ratio of ACE versus ACE2; and the presence of antibodies to ACE2 or its complexes with S viral protein during disease course could help enormously to a better management of diverse pathophysiological abnormality caused by this infectious agent. Some studies in these areas are already begun, where again the use Artificial Intelligence, in the procedural analysis found to be extremely useful [2,3].

The dynamics of changes in heamatological abnormalities

The autoimmune disorders is a well established example of the immune responses often leading to the development of Idiopathic, thrombocytopenic purpura, as a delay autoantibody reactivity response in plasma exchange therapy. In addition there are many bioactive substances that are formed in the early phase of coronavirus infection, such as the activation of the complements and other inflammatory pathways, cytokine storm, and some drop in fibrinolytic potential, leading to hypercoagulability and often to DIC with fatal outcome in severe cases infection. These labile entities need to be taken care of when using convalescent plasma for passive immunity [5-8]. Therefore when creating a passive immunity or vaccine interventional programs for achieving a herd immunity, the procedures and tools used must follow the three R's of best practice "robust, reliable and reproducible" as the holistic approaches, before been applied.

In this context what is missing in the read out of assessing immunity of vaccine or passive immunity, is that we are mainly focusing on the neutralising antibody potency, though apart from by the potency of the neutralising antibody, the T-cell response to this virus is equally important factor, as the two processes often working in conjunction as he two essential pillars of how human immune systems work. In fact in some people who have had the disease, their age related antibody levels could be very low but their T-cell responses might be highly protective than their antibody responses and vice versa. Moreover conceptually the T- cell exhaustion might occur in some for numerous unknown reasons. Hence clearly a lot remained to be yet clarifying about the age –related variabilities in immune systems response to this infection, that remains to be sorted out on the individual basis. Intriguingly the majority of death that currently occurring are in the older populations, though the youngers and asymptomatic infected individual might get long Covid for a period over 6 months at least.

The age-related dynamics in the autoimmune responses of the binding of coronavirus' spike proteins to ACE-2 on cells

Intriguingly the disease dynamics, of this infection is age-related, with some being mainly asymptomatic or mild, while some subset others affected patients experienced a more long–lasting severe complications including multiorgans failure. These long-term complications increase dramatically in over 65 ages, with some comorbidity factors [i.e. respiratory, cardiovascular diseases, obesity, hypertension, diabetes] and subsequent to an exacerbated immune and inflammatory response [1]. Clinically these rebound events are observed weeks, even months, after the onset of symptoms, in some people, when neutralizing antibodies are already present and the viral load is relatively low and the highest IgG, IgA or IgM antibody levels are already present in the critically ill patients. Even more vasculitis are observed in some children who develop a Kawasaki-like disease, all suggesting that it could be the result of immune response to Covid infection, that becomes alloimmune with generation of autoantibodies to some self- proteins, involving in the virus cellular entry complex, acting as physiological antibody's defense systems [1,10-13].

In fact it is well documented that viral binding to ACE2 is essential for both entry to cells and infection progression and the high affinity binding of CoV-2 to ACE-2, through its spike proteins, might lead to induction of the immune response to the self-components involved in the cellular entry through ACE-2 and causing a rebound effect as the consequences of physiological autoimmune alloimmunisation response to infection [1, 14]. While the binding of CoV to ACE-2 for cell entry was previously identified in ARDS, however, the binding of CoV-2 to ACE-2 might have a much higher affinity, in some cases, depending upon the degree of virility infectivity and this could favors the immune system extended reactivity to the whole pathogenic complex, involving viral and self-components [15-17].

The concept of higher affinity binding of highly viral coronavirus is in line with the proposal that some alteration on the ternary structure of ACE-2, exposing the cryptic or hindered epitopes, and contributing to autoantibody generation might occur. Moreover, some acute clinical events, such as the strong inflammatory and complements activations and cytokine storms, the chemo attraction of monocytes and macrophages to multiple pathological sites might be involved [18-19].

The current status of progression on some unresolved immunological/ haematological challenges

In considering to implement passive plasma immunotherapy or vaccination in inducing CoV-2 variant neutralizing activity in timely manner special attention is required on the developments of autoantibodies against ACE-2 as some infected patients is expected to develop an anti-spike autoantibody to ACE-2 and these anti-spike will like ACE2 might contribute to some unresolved age- related questions, for example: a] firstly how ageing influences the function of immune cells and exacerbate coronavirus disease. This concept is also relevant to vaccine response amongst older population, who are already frail and experiencing increased inflammation due to frailty and allowing more bacteria to enter to gut, lungs, kidney heart small intestine brain and skin as the physiological barriers as well as accumulating more senescent cells induced inflammation. Accordingly blocking induced inflammation and the cytokine storms, with Dexamethasone, in the early stages of infection, as it is now becoming routine practices would be understandably highly relevant and promising approach [6]; b] secondly the concept of alloantibody to ACE-2, lead to another question about some long-term infected patients who might have neg antibody tests, because they have robust anti-anti-COVID-19 Antibodies responses, which might questionably mop up most anti-COVID-19 antibodies . Ironically, might anti-COVID-19 antibodies responses render people more susceptible to infection [1].

T-Cell Lymphodepletion in CoV-2 infections and extracorporeal immunosorbent Devices: The major roles played in lymphocytes in the Cronovirus infection can not be denied as there is a close relationship between T cell lymphopenia and the coronavirus infections. In fact both CoV-1 and CoV-2 have been stratified in various ways to measure cumulative [CD4+CD8] counts, using artificial intelligent tools such as: mild to moderate versus severe disease; survivors versus non-survivors; non-severe versus severe cases; and infected patients versus healthy controls.

There are so far several preliminary conclusions: First, the severity of T-cell depletion correlates with a worse patient outcome for CoV-2; Secondly, the degree of lymphopenia appears to associate with an activated hyperinflammatory cascade triggered by the virus; Thirdly, T-cell lymphodepletion may be a surrogate marker of hyper inflammation and has a potential role to identify the timing of when resource intensive clinical treatments such as plasma exchange therapy (PET) that could prevent ICU admissions; Fourthly, the elevated regulatory T-cells (Tregs) that are an important T-cell subset to modulate immune responses and may lower the risk of respiratory viral infections in the elderly. Moreover to attenuate the host inflammatory factors of CoV-2, future development should continue with specialised immunosorbent devices incorporated into extracorporeal circuits for hemopurification. One such product of utility is biocompatible porous polymer adsorbent microbeads. Manufacturers need to become involved to ensure these hemopurification devices in development are secured in the most effective standardised way under strict GMP regulatory adherence [5-6].

Some milestones in the development of vaccines and alternatives as booster therapy

At least 5-6 different vaccine production technologies, amongst many others have been approved for clinical purpose, subsequent to the penultimate criteria of acceptability for medical agency approval. These prodigious and costly research/ development efforts, by multiple manufacturers, are coming as milestones to fruition to save lives. In these endeavors, they have harnessed multiple technologies: (i) mRNA technology using a copy of the spike protein of the coronavirus that has the highest affinity binding sites with angiotensin converting enzyme ACE-2 on the cell membranes, allowing virus to enter into the host cells to propagate; (ii) the conventional vector technologies; and (iii) recombinant protein methods and that successfully used in Russia and China, already in practice in pre-ordered countries, all with excellent safety efficacy outcome.

The current focus is on the most efficient developing manufacturing and distribution programs (DMDP) on a mass scale and currently some validated vaccines have reached their final safety and efficacy evaluations for the prevention of disease. These include the mRNA vaccine candidate BNT 162b2 made by Pfizer and BioNTech (preliminary reported 95% efficacy), Moderna's vaccine (preliminary reported 94.5% efficacy), the Oxford candidate vaccine produced by AstraZeneca targeting the elderly with 90% efficacy at higher investigative dose and the Johnson & Johnson/Janssen candidate that just launched in the United Kingdom, USA and some European communities.

To achieve critical herd immunity globally at 80% requires intensive investment in the infrastructure to optimise vaccine distribution and extensive education of the public at large for vaccination purposes. Surprisingly the oldest aged populations appear to be tolerating well in the oxford 'phase III trials nevertheless the double injection protocols, common to all current vaccines, including the Russian & Chinese types, underscores the importance of investigating the longer-term effects of booster doses of vaccine at the 28-day interval. The

durability of the response, the recommended interval for re-vaccination, ie. Bi-monthly the first two doses and then probably with a longer interval such as 6 monthly or annually depending upon the duration of vaccine effectiveness that remains unknown and to modulate the native vaccine for accrued mutations in the virus structure.

Newer development in production of safer coronavirus convalescent plasma derivatives as the essential part of "Beat Covid" Strategies

Recently in-line affinity column adsorption, blood purifications system and pathogen reduction technologies are planned in view of presence some residual infectious agents including viable Covid antigen, as the essential part of the convalescent plasma therapy. These efforts are aimed to improve the clinical safety of pooled neutralising antibodies [P-NAB] hyper-concentrate, that could be resuspended in appropriately selected available plasma pool containing the balanced levels of all plasmatic active principles, ensuring its optimal effectiveness. This must include optimal levels of albumin, as well as Antithrombin, to be in line with the best practice and with the concept of personalised precision transfusion as often coronavirus patients showed considerable deficiency in these essential proteins, apart from other liver –derived haemostatic parameters.

From the preventative and therapeutics standpoints and on the basis of limitations of vaccines the use of convalescent plasma, as it stands it is justify to create a much safer and standardized products for passive immunity against coronavirus infection. In this context some newer interventional studies for creating safer mode of therapy are highly welcoming for the use of pooled high titer convalescent plasmas or its safer and more efficacious derivatives [5,6]. Apart from convalescent plasma derived from fully vaccinated individuals, in particular this obtained from the AB blood groups, having the highest levels of NAB activities and serum derived from individuals that could not beat CoV-2 variants can be used as the main source of alternative to plasma subsequent to simple affinity adsorption technologies [5].

Such a "Beat Covid Strategies", using CCPD is of particular important for countries with poorer infrastructure, not having access to vaccines, but should be getting training support by well advanced countries with the appropriate know how, for establishing some newer localized design of some cost-effective methodologies for harvesting, and clinical intervention as the best fit locally. The same procedure is applicable to more advanced establishment in emergencies cases where the vaccine fail to provide some measurable levels of neutralising antibodies in poor responders. Nevertheless, despite all these newer initiatives our palates for excellence fall into insignificance when considering the tragic events of numbers of death all over and our heart go out to all suffering family and connection and to our health care front line staff as they have to meet the demand during this crises direct head on.

How we got here and Where we might need be going !

Coronavirus disease has spread globally affecting more than 50 million people worldwide and caused enormous economical and health devastations leading to deaths. Although the majority cases of the infected groups are mild and asymptomatic, but given the staggering number of global infections, and because of the limitations of various preventative or therapeutic agents, the development of new treatment strategies is imperative to improve patient outcomes and attenuate the infection outbreaks. One of the main treatment strategies that has being explored by many internationally, including this investigator, is convalescent plasma. The basic concept of such a plasma immunotherapy is based on the transfusion of previously collected blood plasma from a recovered COVID-19 population of patients to newly symptomatic individuals. While the preliminary data indicates that this therapeutic approach is highly safe and can reduce viral load and improve clinical conditions, but convalescent plasma collection practices and transfusion must be robust and supported by well-designed observational studies, randomised and case-controlled clinical trials to prove on evidence based its superiority over other interventional strategies subsequent to clinical trials.

Currently a well- planned and validated pool of coronavirus neutralising, in cryo-supernatant or viral inactivated SD plasma minipools, as safest plasma derived bioproducts is proposed for prevention and treatment on coronavirus infection, taking into considerations the potential toxicity of CCP. Such a preparation will prove to be of great demand for boosting the levels of the neutralising antibody spontaneously as the circulatory half-life of any CoV-2 NAB, even is when generated optimally subsequent the vaccination after a long delay is relatively short about 4-6 months in most cases. Another useful source of such a purified neutralising antibody is the cadaveric serum of coronavirus patients with prior consent. This means collaborating with some related manufacturers ensuring it is carried out in the most effective standardised way under the c GMP regulatory adherence and using some selected pools and keeping the final products in frozen or freeze dry or spray dry format, to be readily available for use as required a highly useful protocol for developing country with poor economical infrastructure, with no access to vaccines.

Usefulness Artificial Intelligence in the designof of some cost effective tools

Looking into future perspectives, on reflection here again the scope of AI and machine learning in combination with natural human intelligences remains limitless and infinite. In fact with the above objectives in minds more diagnostic development and research in the Beat Covid Strategies domains are still needed, where AI and machine learning will be in great values in big data and patterns and procedural analysis and numerous planned studies in the journey in this direction is already begun [1-5]. In this context, in parallel we should pursue with more rigors the newer insight into the design of some cost-effective methodologies for harvesting, expansion, manipulation and purification of the cultured cells and into the extracellular vesicles involvement in vitro production of reproducible human cells, stem cell extracellular vesicles for substitution therapy and of the antibody delivery on some local sites, as applied for many developing functional materials in transfusion/transplantation that still are amongst novelties in transfusion medicine[20-25].

Noteworthy to mention that from the diagnostic sides some fresher insights from longitudinal plasma proteomics with viral response signature of multiple cytokines and other bioactive materials reveals enormous plasma proteins difference between infected patients and controls as well as appearance of some 200 proteins discriminants between severe and mild groups as a significant diagnostic achievements. Newer flow cytometers tools combined with other tools are currently helping in better characterisation of changes that are occuring [2, 20-23].

However, how long before we could see the real impact of AI and related tools remains the most pertinent question? Can these combined tools effectively and accurately predict properties of newer diagnostic, development and research strategies? Not forgetting the speed and accuracy to be fit for purposes, where a holistic approach is essential in line with best practice and the personalised precision transfusion.

CONCLUDING REMARKS

Since the very beginning of the COVID-19 pandemic, different treatment strategies have been explored to survive this infection and save some live. These mainly involve the development of antimicrobial, antiviral, and/or anti-inflammatory agents combind with some imposed restriction measures at home, at works and how we interct with the others, as well as, the use of some validated vaccines and alternative therapies. The later option should be more avidly investigated as vaccine production on a worldwide level has some short coming, embodying the anti-vaccination movement by anti-vax or nigh % of vaccine hesitancy individuals in many localised communities, that are still real obstacles without yet a ready solutions that have not being tried and of course the vaccine efficiecy that in not 100% and there are always considerable of low or non- responders to vaccines.

This invited commentary was aimed to presents recent findings on the potential therapeutic advantages of heterologous serotherapy for the treatment of CoV-2 variants by proposing not only to highlight the short comings in the effective use convalescent sera against this coronavirus, in view of the presence of autoantibody and some haematological abnormalities as toxic agenents that need to be evaluted and removed before reinfusion but also developing strategies, and protocols for the production of antiCoV-2 sera hyperconcentrates with the promising futures that are effective and free from toxicities that come with the use of the covalescent plasma but indicated to have such as the receptor-binding domain (RBD) in CoV-2 S protein, uopn the ongoing clinical trials. An approach that due to the high death rate, the treatment for those currently infected with coronavirus cannot be ignored.

In this context any vaccines for CoV-2 variants will not instantaneously available and to be accepted as treatment by all people worldwide. The hyperimmune NAB concentrate produced by our simple and most practical technology at a fixed dose in the safe SD plasma or Cryo supernatant for emergency delivery is the best toxic free potent product avaible right now and remains an important therapeutic alternative against CoV-2 prevention and for therapy of infected people with coronavirus, just requiring urgent large scale trials before full implementation.

In short this tiny spiky CoV-2 virus remains as an extravert in terms of personality in styles and its presumed thinking of echoing itself as multiple variants and remixing in variety of forms to get access even the most unvaccinated young population as it the case for the current delta variants joining other variants for optimizing their devastation impacts to vulnerable and leaving behind the long COVID with enormous health impacts embodying the under diagnosed mental heaths both in young and old populations; dementia; eating disorders; and other underlying health issues requiring early social care that need to dealt with some urgency at the early stages . Hopefully with human ingenuity and with perseverance of our youngsters who might finally decide to coming on board we might put an end to this infection by achieving the herd immunity and sooner the better to reach the objective of achieving the herd immunity and focus to overcome the continual health and economical crises and devastation, caused by Cov-2 variants from alpha, through beta and gamma and now to most fearful delta that spreading fast on over 92 countries and the list is still growing exponentially.

It is worthy to highlight that in France there is a combination of south African and Indian delta variants is growing fast, while there are still the alpha variant is ticking along with rigors, an additional worry for the UK, in the shore, that might follow the same patterns. Interestingly now the summer holidays in August in Europe is on brinks now in view of the imported their CoD2 variants .

Clearly we need to find a way to live with Covid variants for time to come and to explore various objectives of helping to convert the unresolved challenges this highly infective tiny virus to opportunity with perseverance, in particular now as in the UK the current imposed restriction policy is coming to end and we must quickly learn as individuals how to coexist with the ever changing nature of the existing CoV-2 strains, just reaching to their peaks in some areas in the UK and others potentially emerging variants, in one of the most vaccinated countries s 70% of adults are vaccinated, despite enormous vaccine hesitancy groups.

Meanwhile the good news is that the production of stem cell therapies requiring high quality, GMP raw materials to be scalable has recently opened a 61,000 sq. ft. GMP manufacturing facility to support large-scale production of

GMP raw materials, enabling therapies to reach more patients. In fact stem cells that are known to moderate defence mechanism is now becoming the key target for new vaccine against COVID variants and could in addition treat the damage caused by dementia, that is the talk of the world, by launching a repair response, hence there is still some lights at the end of tunnel of despair, while still in waiting for a miracle

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