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Commentary

Spotlight on Cov-2 Vaccines and Alternatives for Plasma Immunotherapy and Lessons to Be Learnt From Pitfalls and Successes to Survive the Fast Spreading Indian Delta Variants: Back To Basic and to Future Perspectives

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SUMMARY

This invited viewpoint commentary focussed on attempts made so far to prevent the spread CoV-2 variants infection through the targeted use of some safe and efficacious approved vaccines, combined with some alternative supportive approaches to optimise patient's outcome, teaming up to mitigation and minimising some potential adverse events. In fact the challenges of overcoming vaccine hesitancy, in certain populations, remained unresolved problem worldwide, despite the fact that the team working approaches in the UK mass vaccination, combined with some added interventions and unwanted restrictions, found to be effective to tame the speed viral infection transmission and being highly instrumental in depressing and even breaking the link between infection to hospitalization and viral transmission. Unfortunately delay in imposing boarder restriction timely in the UK, lead to the massive arrival of unwanted imported fast spreading Indian Delta variants, targeting predominantly the younger unvaccinated individual, and the third wave of CoV-2 variants infection in the UK has become a factual reality, causing in delaying the promises of unlocking lockdown, at least until 19 July, so that further opportunity is given to vaccinate younger populations and to extend the total number of double dose vaccination, that is prerequisites now for the optimal viral protection. In short the end is long way out, despite the fact that vaccine hesitancy in the UK is already halved and who knows with the use of different type of targeted multi-variants or mixed matched vaccines and some booster alternatives, that are remaining on the agenda to be deployed, we might be able to beat or survive the newer emerging variants. The journey in this direction has already begun through team working, despite some minor pitfalls on vaccinotherapy, i. e. in the large scale production problems of vaccines in view of pandemic and the strict quality monitoring requirement of labile product at every stages of production; some very rare toxicological complications that regulators had to be judge and jury and don't like to hear about; and some rise in vaccines' nationalism with intense anti-vaccine aggressions to discredit some vaccines by some countries or the profit makers. Fortunately with enormous national sacrifices the UK pre-planned vaccination strategies progressing satisfactorily, despite some hypocrisy and disparity in standards as not everyone following the same rules and recommendations and the delay in traveling restriction from the international hot spot areas. Nevertheless plenty of attributes are deserved for the UK most successful outcomes for making sure that we reached from fictional contributions to factual promises in taming the spread of infection with current available tools, a lesson to be learnt. As for the future perspectives some planned multivariants vaccines and mixed match vaccination and use of some alternatives to stop the emerging variants are still on agenda for deployment but much still remains to be understood on the dynamics of infection and durability of effectiveness of various vaccines and whether polyclonal neutralising antibodies produced by current vaccines are the same than the original CoV2 strains and to those induced by various variants. Our proposed standardised, purified,

polyclonal NAB concentrate free from some toxics substances and viral inactivated, as the safest bioproduct of choice , at least for booster that we need just in time right now, could provide an answer to this question, before the annual cold virus arrive. The core items discussed below are based on some of the ongoing studies and joint publications of this author with some leading international colleagues in this field.

Back to basic on the emerging CoV-2 variants and need for some innovative preventative measures

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, requiring some comprehensive combined infection control measures [1].

The enhanced degree of infectivity of CoV-2 strains appears to be mediated by the virus's S-spike protein and its high affinity binding to the angiotensin converting enzyme (ACE-2) and neuropilin-1 (NLP1) host cell receptors [2-6]. 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 also surfaced in several other countries including the United States, Canada and European countries and the 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 coronavirus CoV-2 epitomizes the perfect example of an unexpected heavy storm that requires prompt rescue plans for the population no matter the associated economic consequences. Needless to mention that a huge numbers of anti-viral, anti-inflammatory, and anti-thrombotic drugs is being recruited to overcome and survive the spread of this infection but with only partial success. Our own ongoing innovative development studies in the use of plasmapheresis-based exchange technologies to decrease inflammatory mediators and in-line affinity column adsorption and to prepare neutralizing antibody concentrate to the virus are still progressing [1,7-10]. This new innovative bioproduct provides some excellent alternative strategies in obtaining the appropriate levels of neutralising antibodies in time to recipient, in contrast to vaccination that takes 3-4 weeks to reach to an equivalent dose and often requiring two doses in such interval duration to be most effective. Such a bioproduct hyperconcentrate is also obtainable from either the pool of convalescent plasma preferentially from male AB blood group, having the highest levels of NAB or from pooled plasma from successfully vaccinated individual timely, reflecting the timely circulating variants [10] and even obtainable from cadaveric serum, if produced at large scale by some interested manufacturers under GMP regulatory compliance anywhere in the world, including in countries with poorer infrastructures and used as the preventative and therapeutic measures and could be also used as the booster for the existing approved vaccines[7-10].

In fact while considerable efforts currently made internationally to collect convalescent plasma by apheresis technologies but evidence is accumulating that the levels of NAB in donors population, after 3 weeks post-test negative, is age/sex and blood groups- dependent and considerable individual variability exist, where the NAB levels in the male AB blood groups being twice higher than the group A and the use of a pool constitutes a more comprehensive approaches for production of the affinity column derived hyperconcentrate, hence the vaccinated male AB blood donations should be systematically encouraged in order to obtain higher levels CCP-NAB and the purified viral inactivated NAB hyperconcentrate mini-pool as proposed by this author [7]. Nevertheless clinical trials, to date, of infected patients have been indeterminate as to whether plasmapheresis-based products are effective or not. This is possibly due to the earlier failures to standardize the composition of the plasma-derived component, for this purpose ; ambiguous clinical indications for use in human subjects and inconsistent timing of administration in the course of the infection. Moreover the known T-cell lymphopenia, which is an attendant to progressive viral infection and immune driven inflammation, and considered to 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 products such as some recombinant proteins and anti-viral drugs [1].

Current position in and development/ deployment of vaccines to achieve herd immunity and the successes and some pitfalls of the current vaccines in use for immunotherapy

Nearly 12 vaccine candidates, so far, are in various stages of approval to achieve the critical herd immunity set at global levels of the above 80%. This means intensive financial investment into the vaccination infrastructure and more importantly in helping some countries with the poorer infrastructure in creating their own localised plants and providing them the supply some of the source materials for the benefit of all in pandemic, as no one is safe until everyone is able to stop the spread of localised variants. The current intent worldwide is not only to optimize distribution but also education of the public and more importantly to emphasize that vaccines are not a panacea, requiring continued vigilance with respect to all personal protection measures.

The current technologies that are being employed amongst many candidate vaccines, harness the same source material [9-13]: (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. Another forward-looking approach is to develop a single efficacious one-dose vaccine, having cost and product distribution advantages. The single dose mRNA Johnson & Johnson/Janssen candidate capitalizes on this approach, and now being approved and in use in USA on the basis of phase III trials in the United Kingdom, United States and European communities. Another trial' vaccine is the innovative booster vaccine 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. Treatment efficacy of the Russian vaccine alone yields 90% [9-10].

The enormous successes of safety/ efficacy and immunogenicity of currently approved vaccines have been subject of many trials before approval and it is well established that all approved vaccines are safe for use and efficacious in the range 62-95%. However it is noteworthy to highlight that the main pitfall of vaccines is that no vaccine is 100% effective in producing neutralising antibodies and we would have only partial success and there will be always some poor or non- responders, requiring the booster neutralising antibodies timely even with the best vaccine –induced durable circulating polyclonal neutralizing antibodies.

In practice however the deployment of the Pfizer and Moderna double dose vaccines have the clear edge in the treatment efficacy, being in above 90% range compared to AstraZeneca [AZ] in the average 70%, in all ages. However, the OAZ double dose vaccine has significant advantages with respect to lower non-profit cost and stability in storage and enumerate several other potential advances in some manufacturing trials such as: combination vaccines such as testing AstraZeneca's product with a component of the Russian's Sputnik V to achieve a superior durable immunity; the production of the first single dose vaccines that have been proven to be effective and currently is in use in USA & Germany as Johnson & Johnson/Janssen to overcome the need for refined thermotolerant formulations obviating the need for cold storage; and establishing new plants in some countries with poorer infrastructure that are in need of huge amount of vaccines as we are witnessing in the India; and having the potential to be used easily as an cost effective adjunct or replacement to vaccine therapy, by using the affinity adsorption technology that is another new facet of convalescent plasmas for countries with poorer infrastructures for processing of coronavirus convalescent plasma or even from vaccine induced development of polyclonal neutralising antibodies against circulating variants timely, when the countries is in urgent need booster antibodies. Nevertheless as for the future perspectives on vaccinotherapy the current focus is still on developing efficient manufacturing and distribution on a mass scale, in view of the enormous demand, despite multiple newly validated vaccines have reached their final safety and efficacy evaluations for the prevention of corona virus disease where follow with Vaccine stability, dosing and timing of inoculations are also crucially important.

These parameters are usually guided by the manufacturer's instructions, the FDA package inserts, recommend 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 warn, are contrary to the accepted science, safety and efficacy data of the recent phase 1, 2, 3 clinical trials in evidence [13].

Neglected high priority groups for vaccination and the rise in long Covid

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 parents, elderly and teachers in close contacts and moreover we should not neglect the younger populations with the long Covid. However some studies already in Arabic countries are carried out with success with the Chinese vaccines for use in adolescents over the age of 12 and more recently the Pfizer vaccine is validated for this purpose both in the USA and Israel with success, despite the benefit versus risk of this approach remained debatable.

Nevertheless 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 Gynaecologists, 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].

Some alternative therapeutic modalities and booster sources of polyclonal antibodies for passive immunotherapy

From clinical standpoint, it is imperative to evaluate the efficacy of the vaccine and all others potential alternatives for the prevention of infection and transmission of the virus, the durability of the response, the recommended interval for re-vaccination, i.e. Bi-monthly for the first two doses and then probably 6 monthly or annually; and if required, to modulate the native vaccine for the accrued mutations in the virus structure. However despite the high efficacy reported for the most promising candidate vaccines, some exceeding over 90%, the remaining 10 % patients still become infected could receive convalescent plasma or even better the hyper concentrate replete with neutralizing antibodies to boost their immune response [7-10].

In fact the use of coronavirus convalescent plasma as a passive mode of the immune neutralising antibodies therapy has gained interest as no specific vaccine against CoV-2 with an acceptable safety and efficacy record had been validated until December 2020 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. Longitudial study of the antibody responses in positive CoV-2 convalescent adults during the first 34 weeks after onset of symptoms revealed that anti-RBD IgG and anti-nucleocapsid IgG levels slowly declined with median half-life of 62 and 59 days

during 2-5 months after symptom onset, respectively and the rate of decline of antibody with the neutralizing capacity diminishes during extended follow-up.

The affinity adsorption bead and or column technology is often used for the preparation of the immunoglobulin hyper concentrate [1,8,9]. 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 and to compensate for the drop in the levels of ATIII due to consumption and synthesis [15]. 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 and even viral inactivated. Only when these component formulations are standardized is it practicable to conduct well-controlled clinical trials as to safest and most efficacious products free from all known toxicological agents of the CCP [1].

In fact the pathogenesis of systemic inflammation, which surfaces with severe respiratory viral infections, has been previously reviewed in the context of treatment and diverse inflammatory mediators consequent to coronavirus infection include disturbances in cytokines, chemokines, and activated complement factors [16-19]. 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 or the viral inactivated SD plasma in the current use and optimise albumin concentrations for infusion purposes and also institute pathogen reduction methodologies to eliminate any residual virus in the former suspension media [1,18,19].

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 activated inflammatory components, microparticles and some autoantibodies and the effects of such antibodies would potentially counteract the benefits of administering the convalescent plasma, [7,18,19].

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. To attenuate the host inflammatory factors 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 micro -beads [20]. Manufacturers should responsibly ensure such hemopurification devices are secured in the most effective standardised way under strict GMP regulatory adherence.

T-cell lymphodepletion and CoV-2 infections is another areas of the current focus. Analysis of published data is reported to address a relationship between T cell lymphopenia and the outcome of coronavirus infections, CoV-2 have been stratified in various ways to measure cumulative [CD4 + CD8] counts: i] mild to moderate v. severe disease; ii] survivors v. non-survivors; iii] non-severe v. severe cases; and iv] infected patients v. healthy controls. Conceptually several clinical outcome could be expected: 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 hyper inflammation 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 [21,22].

Monoclonal antibody, recombinant protein and anti-viral drug therapies is another treatment approaches [1]. 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. 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, as highlighted previously [1,23].

Race between fast spreading Indian Delta/emerging Landa variants and multi-variants CoV-2 vaccines

Our current understanding of the viral kinetics of COVID-19 variants is still incomplete, but the current findings in the UK suggest that the links between the infectivity, transmissibility, and hospitalisation, in all ages, is now broken with the current vaccines in use. Nevertheless, the unexpected appearance of the imported doubly mutated Indian Delta variant, with the highest transmissibility so far, that attributed rapidly to more than 30

million COVID-19 cases and more than 350,000 deaths in India in a very short time, is becoming of a matter of concerns worldwide. Unfortunately only 2% of Indian community is vaccinated hence lacking the immunity, hence enormous devastation in this overpopulated countries and the spread of third wave of infection all over the world, including the UK where about 70% adults are now vaccinated, at least with one dose to provide some degree of protection broadly.

Reduced neutralization of Delta variants but no widespread escape

Evidence is accumulating that the Delta variant (B.1.617.2) is rapidly displacing the Alpha variant (B.1.1.7) as the most dominant variant that contributes to new waves of infection ravaging several countries. In fact the percentage of COVID-19 cases caused by the Delta variant has substantially increased by almost25% in June since its first detection in March but the rate of hospitalizations is much smaller so far and are predominately cover the younger population, indicating that vaccines are working on this variants.

Recent studies on the neutralizing effect of the convalescent and vaccinated serum against the Delta variant confirm that there was some evidence of partial escape of the Delta variant, supportive the notion that : i] The B.1.617 lineage of CoV-2, especially the delta strain that is B.1.617.2 has contributed to the wave of infection in the Indian subcontinent; ii] Structural and serological analyses show no evidence of antibody escape but individuals previously infected with either the B.1.351 (beta) and P.1 (gamma) variants are likely more susceptible to reinfection by the delta strain; iii] Vaccines based on B.1.1.7 (alpha) are likely to provide the broadest protection against current variants and the vaccine/convalescent sera show reduced neutralization of B.1.617.1 and B.1.617.2 ; Sera from B.1.351and P.1 show markedly reduced neutralization of B.1.617.2 ; B.1.351, P.1 and B.1.617.2 are antigenically divergent; and fortunately that both the AZ and Pfizer vaccines based on B.1.1.7 may also broadly protect against current variants diseases.

Targeting blood donors' population for assessing the influence of vaccines on CoV-2 antibodies Seroprevalence

Reflecting however from outside to the inside history, the continual antibody screening of some groups such as targeted blood donors populations for assessing the influence of vaccine on CoV-2 antibodies seroprevalence has been successfully used in Denmark to estimate the number of asymptomatic and undiagnosed cases. Moreover the transmission from children to parents and siblings is became a major concern internationally, because the children are reportedly have either mild or no symptoms, but the question remained of whether in real time they might lead to a more silent disease transmission as many of the repeat donors have small children. Therefore establishing whether there are some hidden cases of SARS-CoV-2 among the blood donors and evaluating the risk of infection posed by a donor at the time of donation became necessary. Clearly using the data easily obtainable from blood donors groups help enormously to collect highly useful data on convalescence time, types of symptoms and antibody levels, and to learn more about the immune response to the virus.

In fact the concept of using this group of blood donors for establishing the neutralizing antibody seroprevalence is excellent from several points of view: Firstly being operationally a rather simple process, and repeated testing of returning donors generates useful data about the duration of the antibody response following infection and vaccination; Secondly provides updated information about the development of the pandemic in the blood donor population, and enable to estimate the number of asymptomatic donors visiting the blood center, helping to evaluate the measures to prevent virus spreading between donors and staff and; Thirdly comparing geographical differences in various blood centers in London with high numbers of immigrants and vaccines hesitancy with others canters nationally and internationally when various types of vaccines are used. In fact evidence is accumulating that, the proportion of blood donors seropositive for anti-SARS-CoV-2 in some blood centers remains stable, despite the number of vaccinated blood donors rapidly increasing. Nevertheless, since the dynamic infection spread changes geographically, as cautionary measures all the health care workers need to be prioritize for early vaccination for providing some protecting against the core variants. In addition, a subset of samples need to be routinely genotyped and ensuring that vaccination is proving successful containment and high degree of protection against Indian variants, by extensive testing, contact tracing and quarantine.

From a broader spectrum looking at the influence of vaccination and other geographical and cultural factors, including vaccine hesitancy, fortunately the states of devastation in the Indian country seems to be on a much better trajectory. New cases have substantially decreased, on average by 53% from the two weeks ago and deaths are down by 35% with the use of vaccines, most of which are being manufactured in India, and slowly making their way to the Indian populations as high priority.

Meanwhile, due to delay in imposing timely restriction on travel from India, this fast-spreading Delta variant, that does not recognise any borders, had plenty of time to establish the third wave of infection in the UK. Although 75% of the adult population in this country are vaccinated, the Indian Delta variant constitutes over 90% of current infections. Intriguingly, they have already caused thousands of deaths in predominately younger unvaccinated and even in some single and double vaccinated individuals though the risk appears to be 20 times lower in double and 4 times less in single vaccinated individuals, respectively. Vaccination appears also to be lowering transmission, and in the race against further spread the vaccination of persons over18 should be intensified, as it is already proving a better immunity. Providing the second dose without further delay now is essential; though it must be remembered that no vaccine is 100% effective, but we need to reach the absolute maximum levels of national immunity. May be the UK vaccination authorities should seek information about combining the Astra-Zeneca vaccine with a second shot of an mRNA vaccine in case this should mount an even more efficient protection from the Delta variant.

Finally it is noteworthy to mention that internationally some vaccination authority are opting for using only the mRNA-vaccines, after the rare blood clot problems associated with the Astra-Zeneca types of vaccine. This is despite the fact that

huge doses of AZ vaccines were injected, before these very rare [one per million] cases of vaccine-induced thrombotic thrombocytopenia were identified. Since today a huge amount of the Moderna vaccines are donated to India as the devastation by Delta variant, while almost reduced by about 50% but continue. Such a comparative analysis would be most warranted, in like with like groups, in particular in female below the age of 30 that are more prone to vaccine -induced TTP.

Despite current limited knowledge on COVID-19 pathogenesis, inflammation, endothelial dysfunction, and coagulopathy appear to play critical roles in COVID-19-associated cerebral small vessel disease that represents a spectrum of pathological processes affecting the brain microcirculation that can trigger subsequent to infection or vaccine induced neuroinflammation a recognized risk factor for stroke. In the background of COVID-19 infection, the heightened cellular activations from inflammations and oxidative stress may result in elevated levels of micro-thrombogenic extracellular-derived circulating microparticles . Consequently, MPs could act as pro-coagulant risk factor that may serve as microthrombi for the vulnerable microcirculation in the brain leading to CSVD manifestations.

Back to future perspectives

The passive immunotherapy, through the targeted use of two originally approved safe and efficacious vaccines, combined with some alternative supportive approaches to optimise the patient's outcome have been effective to survive the spread of CoV2 variants. Nevertheless it is noteworthy to highlight that no vaccine is 100% effective and there will be always some poor and non- responders. Hence in our earlier proposal to use affinity column prepared NAB antibodies concentrates, free from toxic effects, obtainable optimally from the pool of convalescent plasma, or some the vaccinated volunteered individuals timely, to be use at least as alternative booster antibodies stand still firm and deserve to be introduced after a supportive clinical trials. Evidence is also accumulating that COVID vaccines are incredibly effective in real-world settings, illustrating the importance of increasing vaccination rates globally. Meanwhile encouraging news are generated that the two currently experimental vaccines that being developed by Novavax and CureVac on the basis of results obtained in the U.S. and Mexico trials indicating that firstly Novavax's adjuvanted protein subunit vaccine is 90.4% effective in preventing symptomatic COVID-19 disease and secondly 100% effective against moderate and severe disease. Moreover Novavax's vaccine was found to be 90% effective overall in a U.K. study that demonstrated protection against the Alpha variant. Furthermore priming with AstraZeneca's adenovirus vector-based vaccine and boosting with Pfizer/BioNTech's mRNA vaccine induced a robust immune response with an acceptable safety profile in a Phase II trial and the hospitalizations and deaths among older adults in the U.S. have declined substantially following the introduction of vaccines. Similarly both mRNA vaccines and AstraZeneca adenovirus-based vaccine are both highly effective at reducing new Delta variant and induces SARS-CoV-2-specific antibodies that bind more broadly to the receptor binding domain of the viral spike protein than those induced by SARS-CoV-2 variants infection and provides a comprehensive analysis of functional antibody and T-cell responses induced by Janssen's /Johnson & Johnson's COVID-19 adenovirus-based vaccine in a Phase I/II trial.

On the other hands some very rare potential side effect [i.e. one per million cases] such as vaccine- induced thrombotic thrombocytopenia that might be associated with this single dose approved Janssen vaccination, in particular in some groups of female under the age of 50, that are conceptually are most predisposed to hypercoagulability and thrombotic events has becoming accepted as a norm. Intriguingly the rate of vaccination in now is much faster in USA, Germany and France, using this single dose vaccine, despite the huge numbers of vaccine hesitancy and another useful vaccine is added to the list of vaccines, in view of their practical superiority.

Nevertheless so far several millions of 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 by the emerging variants are continuing to rise exponentially, predominately in the younger populations now, facilitated by cohabitation and travel. But vaccination clearly depressing the death despite increasing rate of hospitalisation due to this emerging variants contributing to 92% of all death currently and this is a good news as the colder months approaching soon, so is the rise of the cold viruses. Despite these rising numbers, we should be sanguine about the prospects for a better future. The ongoing mass distribution of multiple vaccines with the perseverance and better understanding tips and tricks of viral mutations and related targeted vaccines, 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. Added to this the targeted use of some newer pharmaceuticals and plasmapheresis technologies to mitigate infections and prevent deaths. Further more we should not to underestimate our resourcefulness and with advancing developmental technologies, and the use of AI tools we should be able to converts newer challenges to opportunities and improve in the future on the evidence based.

Today it is safe to say that Passive immunization with plasma from an early pandemic CoV-2 patient resulted in some significant differences in the outcome of infected individuals that were protected by plasma, B.1.1.7-infected were partially protected, and B.1.351-infected were not protected. Serological correlates of disease were different between infected with B.1.351 triggering significantly altered cytokine profiles than other strains, though the infectivity and immune responses triggered by and observed that early 2020 SARS-CoV-2 human immune plasma was insufficient to protect against challenge with B.1.1.7 and B.1.351.

The evolution of Severe Acute Respiratory Syndrome CoV-2 has been a source of escalating epidemiological alarm in the currently ongoing coronavirus disease pandemic. Mutants of CoV-2 have emerged and appeared to be more infectious and more lethal than the early 2020. The B.1.1.7, variant first identified in the United Kingdom, and B.1.351, first identified in South Africa are the two emerging strains that are rapidly spreading around the world and exhibit high levels of infectivity and therapeutic resistance . Both harbouring significant evolution in the receptor

binding domain (RBD) of the spike (S) viral glycoprotein that are predicted to impact binding to the human angiotensin converting enzyme 2 (hACE2) viral receptor and enhance viral entry to host cells (doi:https://doi.org/10.1101/2021.05.05.44278).

In particular, B.1.1.7 contains the D614G, and N501Y, mutations in the CoV-2 S RBD which are theorized to increase the ability of the virus to bind to h ACE2. B.1.351 possesses these key mutations in the S RBD, in addition to the K417N mutation E484K mutation which are not directly implicated in altered viral transmission and hACE2 binding. The culmination of high infectivity, therapeutic resistance, and key changes in the viral genome suggests that these variants on concerned may have an impact on pathogenicity and could have an impact on evaluating CoV-2 pathogenesis as well as prophylactic (vaccines) and therapeutics (antivirals). It is possible that K18-hACE2 individuals infected with CoV-2 exhibit significant morbidity and mortality, viral tropism of the respiratory and central nervous systems, elevated systemic chemokine and cytokine levels, significant tissue pathologies, and altered clinical outcomes.

As the number of CoV-2 variants is increasing in the world it is imperative to adapt existing preclinical animal infection models to these newly emerging variants to better understand if the K18-hACE2 first in the infection dynamics and second, if it exhibits any differences after challenge with newly emerged variants for developing new therapeutics and prophylactics as the COVID-19 pandemic continues to emerge.

Clinical studies of therapeutics and vaccines for COVID-19 have been complicated by the rise of CoV-2 variants. Therapeutic escape by these mutants is already documented and requires the development of novel treatment options as well as re-evaluation of existing ones. One of the first treatment options for COVID-19 was infusion of convalescent plasma that exhibited some beneficial effects early in the pandemic for critically ill patients but its utility has recently been called into question in view of speculations as to the reasons behind this, including that neutralizing antibodies (nAbs) generated against the CoV-2 S RBD may have different affinity to the new variants. But as many therapeutics and vaccines have focused on the RBD or S protein of Cov-2, it was of interest to determine whether early pandemic convalescent plasma containing neutralizing antibodies against earlier CoV-2 S RBD protects against these new variants with mutations in their RBD. Thus to determine whether theses Variants can evade an early COVID-19 pandemic therapeutic via newer affinity column derived NAB concentrates either from CP or timely successful vaccinated individual as the nature of the polyclonal NAB produced might expectedly be different. Much to remains to be resolved to turns many unresolved challenges to deserving clinical opportunities.

Intriguingly, current laboratory data indicate that both OAZ and Pfizer BioNT

Induce lower levels of antibodies targeting the Delta variants and this trend is most marked for the Pfizer-BioNTech vaccine than the OAZV being 2.5 times lower suggesting that the Levels of antibodies alone do not predict vaccine effectiveness, however the two doses of either vaccines are essential to boost antibodies to quantifiable levels that are likely to maximise the amount of protection against severe disease and supress the hospitalisation. Moreover antibody levels induced by the OAZV vary considerably depending on people who had previously reported having symptoms of Covid-19, showing higher antibody levels after their first vaccine dose than those who did not report symptoms and did not know if they had Covid-19 previously. Hence providing further insight into which groups of people are most at risk, and might require an additional booster vaccination or alternatives.

In fact in animal study to test the ability of antibodies to block entry of the virus into cells, so called 'neutralising antibodies', against five different variants of CoV-2 strains and then compared concentrations of these neutralising antibodies across all variants, and found that the fully vaccinated with two doses of the Oxford-AstraZeneca vaccine, nearly all had a quantifiable level (87% with >40 titre) of neutralising antibodies against the variants previously dominant in the UK (D614G and B.1.1.7). But significantly fewer had quantifiable levels against the Beta and Delta variants (60% and 62% respectively). This contrasted with the Pfizer-BioNTech analysis, which showed that over 95% of recipients had quantifiable neutralising antibody levels against the Beta and Delta variants after both doses.

A significant proportion of people without prior Covid-19 symptoms had antibody levels below the limit of detection against new variants of concern (65% against B.1.1.7; 88% against B.1.351; and 85% against B.1.617.2). This variation was not seen in recipients of the Pfizer-BioNTech vaccine.

The people analysed in this part of the study were younger than average Oxford-AstraZeneca vaccine recipients (median age 34), so more research is needed to understand the antibody response in older people. Clearly as no vaccine is 100% effective, if more individual are fully vaccinated the chance of bringing down the spread of this new variant under control would be greater. This also would clearly help us to understand which groups of people are most vulnerable and prioritise them for boosting in the near future perspectives.

In short our current understanding of the viral kinetics of COVID-19 variants is still incomplete, but the current findings in the UK suggest that the links between the infectivity, transmissibility, and hospitalisation, in all ages, even for the unexpected appearance of the imported doubly mutated Indian Delta variants, with the highest transmissibility so far, is now enormously suppressed and even broken with vaccines in the current use. This brings about to reflect on the third wave of infection and on targeting blood donors 'population for assessing continuously the influence of vaccines on CoV-2 antibodies seroprevalence that provide, for many operational reasons, a good estimate of the number of asymptomatic and undiagnosed case and helping in better understanding of long COVID is very little known about and how long lasting the vaccine induced immune system, even with the second dose and possibly the third booster dose persist. Clearly it is timely to better understand that if differing vaccine - induced high affinity neutralsing antibodies differs between themselves and differ from various variants induced neutralising polyclonal antibodies.

Needless to highlight that any negativity of either politically or commercially-driving natures or by the most active negative viewpoints of most active anti- vaccine lobby on any vaccines, as we have been witnessing mainly to AstraZeneca of vaccine, that is known the cheapest world vaccine and most practical vaccine, would have some bearing on vaccine hesitancy adding some additional challenges for the world seeking to achieve the herd immunity. So far at least in the UK vaccination were based on the most cautionary measure on the basis of the risk benefit analyses in adults, top down age and the most vulnerable to protect them successfully, where AstraZeneca vaccine proved to be excellent. Now the attention is focussed on youngsters and children as well as the booster jabs that need to be given before the winter season for additional security, where the risk benefit are almost equivalent and we are unlocking the restriction. Here come the moral failure issue for the public health reducing risk coming from other countries that are poor vaccinated[less than 2%] in view of the luck of access to vaccine. The way forward is to help the others in sprit of oneness and to stop the import of new variants right now as the most beneficial approach as no one is safe until the world is safe.

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