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Editorial

Do highly transmissible omicron subtypes BA.4/BA.5 have any impact on the HLA class I /II antibodies of apheresis donors, and could mucosal omicron-specific vaccines prevent transmissibility and provide more durable protection?

Editorial commentary

The HLA-specific antibodies are a major risk factor in inducing TRALI that is responsible for most transfusion-related deaths. Both SARS-CoV-2 infection and vaccination effectively stimulate a general immune response and could potentially induce *de novo* production of antibodies to HLA class I/II in patients. This may complicate the treatment options for immune-mediated platelet refractoriness in multi-immunized patients and increase the need of HLA-matched apheresis platelet therapy. In addition, an increased number of platelet donors producing HLA-antibodies would further jeopardize the availability of HLA-matched platelets. It is therefore imperative to explore whether the specific HLA-antibodies number is elevated in the apheresis blood donor groups that are well-characterized with regard to their serological and immunological status and thoroughly reflect the young and middle-aged adult populations in the national communities. These groups may be more exposed to viral infection in real time, through social and community encounters.

In this issue, as a follow-up, I have invited Doctor Lise Sofie H Nissen-Meyer, from Department of Immunology of Oslo University Hospital, Norway, to share with us the result of their comparative studies on the HLA class I/II antibodies of healthy apheresis donors, following the first wave of coronavirus infection [alpha/delta] or classical SARS- CoV-2 vaccination. In short, in their original observational study based on 106 Norwegian apheresis donors, Nissen-Meyer et al. compared the data on the levels of antibodies to HLA class I/II following Covid-19 infection and vaccination, with data available from pre-Covid blood samples. They concluded that SARS-CoV-2 virus or vaccination have no particular impact on the *de novo* HLA immunization in representative groups of healthy apheresis platelet donors. However, for some donors pre-existing antibodies were strengthened, confirming a general boosting of the immune response following infection or vaccination. However,

However, in the light of changes in the characteristic properties of these highly transmissible omicron subtypes BA.4/BA.5 and the use of more specific booster vaccines, it remains to be established if the overall outcomes might differ.

Development of virus subvariants

Today, the newer, heavily mutated omicron subvariants have predominantly overtaken all the earlier variants, from alpha to delta. The original South African omicron variant, BA.1, was much more infectious than any known subvariants when it appeared, but was quickly outpaced by the BA.2 subvariant earlier this year. Then came BA.2.12.1, which was closely related to the BA.2 subvariant. This was followed by BA.3 in South Africa that had no significant impact on mortality. The latest subvariants so far, also first identified in South Africa and named BA.4 and BA.5, are causing a new uptick in COVID-19 cases; they are now circulating in at least 63 countries and are considered to be the most dominant strains in the US and the UK.

Interestingly, there is no evidence yet that these latest omicron subvariants cause more severe disease, as only a small increase in hospitalizations and deaths occurred when these variants were at their peak in South Africa. However, this pair of subvariants did cause a notable increase in hospitalization rates in Portugal, where vaccine effectiveness against severe disease has been dropping with the rise of each new viral variant. With the extent of BA.5′s immune evasion and the recent trends of lowered protection from severe disease, vaccine effectiveness changed from 95% (vs. delta with a booster), to approximately 80% (vs. omicron BA.1 or BA.2 with a booster). A recent comparative analysis revealed that the median neutralizing antibody titers are lower by a factor of 6.4 against BA.1, by a factor of 5.8 for BA.2, 9.6 for BA.2.12.1 and 18.7 for BA.4 or BA.5. These data support the notion that the BA.2.12.1, BA.4 and BA.5 subvariants substantially escape neutralizing antibodies induced by both vaccination and infection [Source: G medicine]. The increased neutralization escape developed in the BA.4 or BA.5 subvariants is in an immunologic context relevant to the current surges of infection in populations with high frequencies of vaccination, such as the US and UK.

The reported changes in the structural sequences of the omicron variants embody: a] first, all omicron variants contain L452 mutations and lack the G496S mutation. This gives them higher transmissibility, increased ability to bind the ACE2 receptor and helps them to escape the immune response; b] Secondly, the introduction of F486V and the loss of Q493R in omicron BA.4 and BA.5 further decrease the hydrophobic nature of their interactions and significantly reduce the efficacy of existing booster vaccines. The lingering question that remains to be explored is “the process capability index”, i.e., whether these more transmissible variants influence the immune response to a greater degree than the earlier SARS-CoV-2 variants.

Vaccine development

The first series of the authorized COVID-19 vaccines exceeded all expectations. The mRNA-based shots from Moderna and Pfizer/BioNTech, and also the vector-based vaccine from Astra-Zeneca, worked

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remarkably well at preventing severe disease and death from COVID-19, meeting the ultimate goal of vaccination. They also were relatively effective at preventing infection altogether with the earliest strains of SARS-CoV-2. Breakthrough infections nevertheless might occur in individuals with a weaker antibody response, even after booster immunization. This is possibly due to a low level or poor binding and /or poor neutralization capacity following booster vaccines.

Last week an external committee of expert advisers recommended that the FDA should authorize the updated versions of COVID-19 vaccines, based on the omicron variant. These include: the one made by Pfizer/BioNTech (Comirnaty) and the other by Moderna (Spikevax). The updated vaccines would be used as boosters and would likely become available this fall, when experts warn that another wave of infections is probable - given both waning immunity and cooler weather.

Interestingly, a preprint study from Moderna shows that their bivalent booster, which is based on SARS-CoV-2 Spike proteins from both the ancestral strain of SARS-CoV-2 and the BA.1 omicron variant, induced a superior neutralizing antibody response against BA.1 as compared to the original monovalent vaccine based only on the ancestral strain. Although BA.1 has already been replaced by BA.4 and BA.5, the BA.1 booster would likely still have benefits, including broadening immune responses and providing some degree of enhanced protection against severe disease. However, the above committee of experts seemed to favor using a BA.4/BA.5 omicron-based booster, while debates are continuing about who would be eligible, and which omicron-specific boosters to use. Some are suggesting that high-risk groups would likely be the primary focus, while others pointed out that none of the studies of these boosters are being conducted in children, who therefore would not be initially eligible.

More than a dozen vaccine candidates for oral or intranasal administration are already in clinical trials, and several others in preclinical development. The next-generation of COVID-19 vaccines and their improved modes of administration are appearing much faster than expected, as there is an appetite from both manufacturers and suppliers of vaccines and government to put money toward this goal.

According to Moderna, their bivalent vaccine cocktail is effective against omicron sub-variants BA.4 & BA.5. Sanofi/GSK data has shown their shot to confer protection against the omicron variant of the virus, while Pfizer released a study of more than 1200 adults who spurred a substantial jump in omicron-fighting antibodies after receiving its newest vaccine. Moreover, the prime-boost vaccine combinations increased neutralization titers to the omicron variant, as the boosted titers declined rapidly compared to those against the prototypic D614G variant. Some pan-coronavirus vaccines are also in development in order to be more variant-proof options and could eliminate the need for repeat booster doses altogether.

Interestingly, the omicron targeted mRNA mucosal vaccines are showing incredible efficacy (~95%) against severe disease as well as reducing transmission. Indeed, promising results towards the goal of these vaccines providing protection against infection. In the current muscular administration of the original SARS-CoV-2 vaccines, limited mucosal immunity is induced in the respiratory tract, in particular in the nasal cavity and the lung, the major infection and transmission sites. According to Benjamin Israelow, Yale University of Medicine, the direct priming and spiking in the mucosa in this mode of vaccine administration leads to a better antigenic access to these sites, thus increasing local antibody production and cellular defence mechanisms.

This is of particular relevance right now, in real time, as this week in the UK, about 1.7 million individuals, as compared to 1.4 million in the last week, are infected with the omicron variant B.A 4 and B.A.5. There is also some significant rise in hospitalization and even death, particularly in the older age group, despite the use of a fourth Moderna booster dose.

Differential patient immune responses to infection or vaccine

From the clinical laboratory point of view, a recent report highlighted an inferior humoral and sustained cellular immunity against both wild type and newer omicron variants of concern in hemodialysis patients immunized with 3 doses of SARS-CoV-2 vaccine as compared with 4 doses [Source: Med Global]. Despite the use of fixed validated booster doses of the relatively "omicron-specific" vaccine from Moderna (currently in trials in the UK), a new surge of omicron sub-variant BA.5 has emerged, predominately in some part of Scotland and in London. High vaccination levels probably exert selection pressure on immunity-evading subtypes, as explained above. If the observed tendency of increased spreading capacity is combined with – or a consequence of – reduced immunization properties, at least the fear of irrelevant antibody boosting can be relaxed. Clearly, life under the influence of newly emerging heavily mutated omicron ghosts remains full of uncertainty. The race against this fast-mutating virus with its unmatched ability to escape all defence systems may, perhaps, never be won by human expertise. One comfort, though; the risk of developing" long COVID-19″ appears to be much lower in individuals infected with the omicron variant of SARS-CoV-2 than in those infected with the initial subvariants.

Measuring the individual variability of pre-infection antibody titers and its neutralization capacity could provide an easy tool to estimate the risk of developing omicron infection. Currently, testing of anti-SARS-CoV-2 antibodies or neutralization capacity is not routinely performed after vaccination. Performing testing combined with setting some agreed thresholds for SARS-CoV-2 IgG antibody levels would help to identify "non"-, "low"- and "high"- responders. This approach has been recently used for re-vaccination of individuals with weaker antibody responses after booster immunization of elderly or immune-compromised individuals [Source: Frontiers in immunology]. Also, the interval to re-vaccination in individuals with high response might be extended. Further studies are needed to develop a more effective vaccination strategy in these groups, independent of vaccination scheme, gender, age and habits.

However, it is prerequisite to examine the immunogenicity, antigenicity, and pathogenicity of SARS-CoV-2 variants in both vaccinated and previously infected individuals. By analyzing the SARS-CoV-2 variant recognition, dynamics of memory B cells, and secreted antibody levels over time following natural infection, vaccination, and boosting, researchers are identifying how monoclonal antibodies neutralize SARS-CoV-2 and how the neutralizing activity against SARS-CoV-2 variants of concern can be magnified.

Lifting our eyes to new developments

Clearly, we must invest in our preparedness and readiness to enhance our defence systems, with all innovative diagnostic, development and research (DDR) tools, and combining artificial intelligence with human intelligence to target best practice in vaccination programs. We also need to learn more about "long COVID", and ways to crack down or put in place some deterrents in the imported variants, in the context of saving lives. It is also important to examine the interaction between population immunity and viral dynamics to better understand the SARS-CoV-2 susceptibility and transmissibility. Moreover, some in depth education programs at the community levels are essential; there are still numerous vaccine hesitant groups, highly prone to infection, who potentially might delay the goal of maximum immunity, at least in heavily vaccinated countries. A look at anti-vax propaganda can take the courage from us all.

The good news is that there are several collaboration platforms that allow scientists, manufacturers and physicians to post a clinical dilemma and get answers from verified sources in the relevant specialty, thus using the power of the global medical community to shorten the diagnostic time and improve health care. Interestingly, some manufacturers,

such as GSK, plan to invest £1 billion over the course of 10 years into research on infectious diseases that largely affect low-income countries, and from the vaccine supply side, the pharmaceutical company, Moderna, will set-up a manufacturing and research development center in the UK following an agreement with the government. Unfortunately, few initiatives are taken for the countries with poor economics that are most in need – besides, there is an urgent need for globalization efforts to end this pandemic.

IN SHORT, to answer the two initial questions: a] Considerable advances have been made towards a better understanding of the characteristic profiles and the "process capability index" of omicron subvariants, but much still remains to be established in regard to prevent the emerging subvariants transmissibility and to provide more durable protection; and b] whether infection with the heavily mutated omicron variant or vaccination, that effectively stimulate a general immune response, could potentially induce *de novo* production of antibodies to HLA class I/II in patients; we need to wait for a more comprehensive report - from Norway, or some interested Trasci readers, in the coming issues.

I wish to take this opportunity to thank Nissen-Meyer et al. for sharing their insights and experiences on the current scope of HLA class I /II antibodies in healthy apheresis donor groups with our readers, serving as a model example in the article to follow; and also, for helping me as part of a real team, to deliver quality content for this regular section of the journal.

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