ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

https://ijmsweb.com

Indian Journal of Medical Sciences

Viewpoint

Current challenges and controversies surrounding SARS-CoV-2 immunity and their implications on reinfection, plasma therapy treatment outcomes, and vaccine development

Vishal Rao[1], Swetha Kannan[2], Anand Subhash[1], Gururaj Arakeri[1], Ashish Gulia[3]

[1]Department of Head and Neck Surgical Oncology, HCG Cancer Hospial, Bengaluru, Karnataka, India, [2]Department of Immunology, School of Biological Sciences, University of Edinburgh, Old College, Edinburgh, Scotland, United Kingdom, [3]Bone and Soft Tissue, Tata Memorial Hospital, Mumbai, Maharashrta, India.

ABSTRACT

The global pandemic of coronavirus disease 2019 (COVID-19), caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was recognized using of next-generation sequencing. The pandemic is associated with respiratory distress syndrome, hyperinflammation, and high mortality making it a major public health concern. It is essential to explore the pathogenetic pathways to conclude a definite therapeutic approach. However, the crisis of the COVID-19 pandemic altered the equilibrium between waiting for substantiating results before determining whether to use the therapy or generating evidence during regular patient care, in support of the second choice. This review describes various key controversies and challenges of SARS-CoV-2 immunity, convalescent plasma therapy, and treatment outcomes. It further highlights the emerging vaccine therapy and future strategies for the treatment of COVID-19.

Keywords: COVID-19, Immunity, Plasma therapy, Vaccine

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), also known as coronavirus disease 2019 (COVID-19), has emerged as a serious pandemic infecting about 17 million humans and causing nearly 7 lakh deaths worldwide.[1] SARS-CoV-2 reportedly originated in wet markets of Wuhan City, China, in December 2019. Since then, it has spread to many countries and impacted global economy and employment, bringing the world to a standstill. Viral transmission among the human population occurs primarily through aerosol and fomites.[2] The novel coronavirus, on entry into the human body, induces a severe acute respiratory syndrome, termed COVID-19.[3] Nearly 80% of individuals infected by the virus present with asymptomatic or mild forms of COVID-19, while about 20% progress to severe stages of the disease, often requiring ICU admission and ventilation.[4] Immune responses play a key role in governing the clinical evolution and progression of COVID-19. In the absence of a registered vaccine, current therapeutic interventions for this disease include antiviral agents and immune modulating treatments.[5]

While the role played by humoral and cell-mediated immune responses in other viral infections have been well-characterized, scientists and clinicians are still struggling to understand these immune responses in the context of COVID-19. This review paper describes some of the key controversies and challenges surrounding SARS-CoV-2 immunity that modern medicine is trying to address. Finding solutions to these challenges would offer clinicians and researchers with a more holistic insight into the etiopathology of this infection, aiding vaccine design and the drug development.

ANTIBODY RESPONSES

Antibodies play crucial roles in combating viral infections. Humoral immunity against a virus is usually achieved a result of direct antibody-mediated responses that interfere with viral entry and replication into host cells, as well as indirect ones that facilitate communication between innate and adaptive immune cells, warning them of the presence of a viral pathogen and virally infected cells/tissues.[6] To successfully combat viral infection, these virus-elicited antibodies in individuals must engage in surveillance and protection against current infection and potential reinfections.

***Corresponding author:** Vishal Rao, Department of Head and Neck Surgical Oncology, HCG Cancer Hospial, Sampagni Rama Nagar, Bengaluru - 560 002, Karnataka, India. hnresearch@hcgel.com

Received: 09 September 2020 **Accepted:** 17 September 2020 **EPub Ahead of Print:** 17 November 2020 **Published:** 24 September 2021 **DOI** 10.25259/IJMS_272_2020

A recent study by researchers at King's College London reported that SARS-CoV-2 antibodies rapidly declined in patients, falling to nearly undetectable levels in some patients 2 months post-infection.[7] IgM and IgA levels witnessed a more rapid decline in comparison to IgG levels, which were found to remain at heightened and detectable levels for nearly three in most patients. Interestingly, when these results were compared on the basis on symptom severity, the previously described heightened levels of IgG antibodies were undetectable 60 days after symptom onset in a few patients who had experienced mild symptoms.[7] The researchers also discovered that patients with milder forms of infection had fewer antibodies at their peak. Such patients, with diminished peak antibody levels, were more likely to present with undetectable levels of these antibodies after 60 days.[7] It is also interesting to note that not all individuals who present positivity in diagnostic molecular test results have detectable levels of IgG.[8] Moreover, neutralizing antibody levels in some patients are almost undetectable.[9] These findings bring to light important concerns surrounding protective immunity and the duration for self-isolation/quarantine.

Neutralizing antibodies are a class of antibodies produced in response to viral attack and function to block viral entry into host cells. Several studies have reported that NAb levels remain high for a few weeks post-infection and eventually begin to decay.[10] It is now known that individuals with a more severe form of infection present higher levels of NAbs in their sera in comparison with those who with milder or asymptomatic infections.[11] It is speculated that the higher viral load in individuals with severe infection results in the generation of a greater number of antibodies which last for long periods of time. However, what we still do not understand is what levels of these neutralizing antibodies are required to prevent SARS-CoV-2 reinfection. At present, there are no available effective assays to determine these levels of neutralizing antibodies in patients/donors, due to restrictions including the requirement of a live virus and BSL-3 facilities.

Keeping these findings in mind, some of the most important questions surrounding antibody responses in SARS-CoV-2 that currently remain unanswered and require further research and clinical validation include:

1. Do antibody responses play a role in why some infected individuals only present mild symptoms or are asymptomatic, while others suffer from a more severe infection? Do these responses also govern disease progression and recovery, if so, to what extent?
2. Why are delayed and weaker antibody responses associated with severe clinical outcomes?
3. Why do not positive diagnostic test results always correlate with presence of IgG and neutralizing antibodies?
4. Is the quantification of antibody levels actually an effective way of monitoring SARS-CoV-2 immunity?

From the current data, asymptomatic individuals and those with milder form of infection seem to be at a higher risk of reinfection on account of rapid antibody decay. Whether the presence of cell-mediated immune responses, such as those mediated by virus-specific T-cells confers long-term immunity in these individuals in the absence of antibodies, requires further research and validation. There might also be other classes of antibodies, in addition to NAbs which may play a key role in combating SARS-CoV-2 primary and secondary infections.[12] A group of researchers at the University of Montreal has proposed to study the role of antibodies that bind to infected cells and mark them for execution by immune cells – a process called antibody-dependent cellular cytotoxicity – in responses to SARS-CoV-2.[12]

CELL-MEDIATED IMMUNE RESPONSES IN SARS-COV-2

From the above discussion, it is quite clear that antibody responses are only part of the picture. Cell-mediated immunity in the form of T-cells, which can identify and kill cells infected by a pathogen, is another typically long-lasting element of immunity. Hence, it is possible those who have been infected, but have negligible antibodies, have some T-cell-based resistance to SARS-CoV-2. A recent study conducted in Sweden, reported that despite testing negative for SARS-CoV-2 antibodies, patients are likely to have active T-cell responses against the virus.[13] However, whether this T-cell immunity is likely to prevent reinfection and provide long-lasting protection against the virus is something that requires further research. The interaction of humoral and cell-mediated immunity and their respective longevity against SARS-CoV-2 requires more research, especially in context of the ongoing vaccine trials and our theories of herd immunity. In an attempt to understand the interplay between cellular and humoral responses specific to SARS-CoV-2, researchers recently identified an interesting correlation between NAb titers with the number of virus-specific T-cells.[14] Although this requires further validation, these preliminary findings do guide us to the interesting possibility of whether virus-specific T-cell levels could be used as a surrogate marker of SARS-CoV-2 immunity in patients. The use of these cellular assays would help overcome the limitations posed by typical NAb assays, since they do not require the presence of a live virus or BSL-3 facilities. It also leads us to speculate if T-cell transfer therapies, such as those used in cancer immunotherapy, would be a better therapeutic intervention in critical cases in comparison to plasma therapy.

Some of the most important questions surrounding cell-mediated immune responses to SARS-CoV-2 that currently

remains unanswered and requires further research and clinical validation include:

1. Do cell-mediated immune responses play a role in why some infected individuals only present mild symptoms or are asymptomatic, while others suffer from a more severe infection? Do these responses also govern disease progression and recovery, if so, to what extent?
2. Is quantification of virus-specific T-cells through cellular assays actually an effective way of monitoring SARS-CoV-2 immunity? If yes, would T-cell transfer therapies, serve as better therapeutic interventions in critical cases in comparison to plasma therapy?
3. Could inflammatory markers such as cytokines and chemokines function as reliable predictive markers of SARS-CoV-2 immunity?

At present, due to the absence of a specific, measurable marker that correlates with long-term immunity, it is important to holistically understand different kinds of immune responses and draw comparisons with other viral infections to draw conclusions on the duration of protective immunity.

IMPLICATIONS FOR PLASMA THERAPY

Recent studies have reported moderate success rates with convalescent plasma therapy (CPT) for SARS-CoV-2 infections.[15] CPT involves the collection of sera from individuals recovered from SARS-CoV-2 and its administration to severely ill patients currently battling the disease. It follows the principle of "Passive immunization." Individuals who have recovered from COVID-19 would have mounted an adequate and effective anti-viral immune response and generated strong humoral (antibody mediated) immunity and immune memory against the virus. These individuals are thus likely to contain a large pool of neutralizing antibodies against SARS-CoV-2 in their plasma.[16] This plasma, when isolated, could be administered to severely ill patients and help boost their ability to fight the virus by aiding eradicating the pathogen from blood circulation and pulmonary tissues.[16] However, to determine the success rate of CPT, it is crucial to understand the effectiveness of the donor plasma in neutralizing the viral particles in the recipients' body.

At present, there are no available standardized protocols in place for screening donated plasma for neutralizing antibody levels. This results in variability in SARS-CoV-2-specific antibody levels in donor plasma, which can then impact the effectiveness of CPT. While several studies have argued that CPT might prove to be an effective form of treatment for COVID-19 patients, a recent study by the ICMR, awaiting peer review, reported that administration of convalescent plasma in hospitalized patients did not correlate with reduction in mortality or progression to more severe forms of the illness.[17] At present, available clinical data are inadequate to make any definitive conclusions on whether CPT can be considered as a potential cure.

Some of the most important questions surrounding plasma therapy that currently remains unanswered and requires further research and clinical validation include:

1. How effective is the administration of CPT in enhancing recover rates of severely ill COVID-19 patients?
2. Are serum antibody levels (IgG, IgM, and NAbs) reliable predictive markers of CPT efficacy? If so, what are the isotypes of antibodies that specifically correlate with must be screened for? What are the levels of these antibodies required in donor sera pre-transfusion, and how do we accurately quantify them?
3. In the absence of antibodies in donor serum, can cellular response assays such as those mentioned above be used as a predictive marker for CPT outcomes?
4. How does the previously discussed decay in antibody levels influence CPT outcomes? What is the duration of immunity conferred upon administration of CPT?

IMPLICATIONS FOR VACCINE DEVELOPMENT

Evidence from recent studies reveals that SARS-CoV-2 is broadly similar to the four coronaviruses that cause about one-third of all common colds.[18] Several experiments in the past have established that protective immunity to these cold-causing coronavirus strains is short lived.[19] The established similarity between these coronavirus strains and the short-lived protective immunity against them strongly suggests the possibility of SARS-CoV-2 becoming a seasonally recurring pandemic. In such circumstances, the development of an effective vaccine against the virus becomes a serious challenge.

Current data in humans suggest that SARS-CoV-2 vaccines are likely to trigger immune activation and the production and release of neutralizing antibodies that function to inhibit viral entry and infection. However, drawing on points from the above discussion, what remains unclear is whether the produced levels of these antibodies are high enough to confer preventive immunity and protect individuals from new/subsequent infections and the duration of their persistence within the body. Furthermore, recent research has brought to light the possibility of SARS-COV-2 proteins evolved to become weak immune stimulants.[20] This then poses a problem for current SARS-CoV-2 vaccine candidates (mostly RNA vaccines) using natural variants of SARS-CoV-2 viral proteins as antigens. A higher success rate is more likely with other forms of vaccines such recombinant vaccines that employ the use of genetically engineered viral antigens or T-cell vaccines that function to trigger cell-mediated immunity against the virus through a robust memory T-cell response.

Immune enhancement is another important factor to consider during the design and development of COVID-19 vaccines.[21] There are several mechanisms that govern immune enhancement due to vaccines, the most well-established being ADE or antibody-dependent enhancement. In ADE, antibodies typically confer protection against a specific viral strain, and when challenged with a slightly different viral strain, bind to the viral particles without effectively neutralizing them. Since these antibodies are not able to disable the virus, they play a key role in helping them establish stronger, systemic infections in the host which may in certain cases lead to death.[20] Such phenomena are yet to be studied in the context of COVID-19 vaccines.

Some of the most important questions surrounding SARS-CoV-2 vaccine development that currently remains unanswered and requires further research and clinical validation include:

1. Are the levels of NAbs produced by current vaccine candidates high enough to confer preventive immunity and prevent new infection?
2. What is the duration of immunity conferred by current vaccine candidates that trigger NAb production and release?
3. Are cell-based vaccines such as T-cell vaccines a better alternative to RNA-vaccines?
4. Are ADE or other forms of immune enhancement likely to occur on administration of antibody-based vaccines?

CONCLUSION

It is now 6 months into the pandemic and there are still several questions, such as those highlighted above, that scientists and clinicians are making sustained efforts to answer. It is thus, extremely vital to keep the these questions in mind and understand their relevance to specific aspects of SARS-CoV-2 immunity and therapeutics, to gain clearer and more realistic insights into the impact of the COVID-19 on individual and public health. Finding answers to these questions would help physicians and researchers better assess into the etiology and immune pathology of this infection, aiding effective vaccine design and the drug development.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest. The author Ashish Gulia is the editor of this journal. He does not have any competing interest.

REFERENCES

1. Gupta N, Praharaj I, Bhatnagar T, Thangaraj JW, Giri S, Chauhan H, *et al*. Severe acute respiratory illness surveillance for coronavirus disease 2019, India, 2020. Indian J Med Res 2020;151:236-40.
2. Agarwal N, Biswas B, Nair R. Ensuring safety and availability of healthcare workers in the era of COVID-19: An experience from the Eastern State of India. Indian J Med Sci 2020;72:58-64.
3. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, evaluation and treatment coronavirus (COVID-19). In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2020.
4. Lai CC, Liu YH, Wang CY, Wang YH, Hsueh SC, Yen MY, *et al*. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths. J Microbiol Immunol Infect 2020;53:404-12.
5. Bhuiyan MN, Ganesh R, Ghosh AK. COVID-19: A 2020 update. Indian J Med Sci 2020;72:88-94.
6. Shishido SN, Varahan S, Yuan K, Li X, Fleming SD. Humoral innate immune response and disease. Clin Immunol 2012;144:142-58.
7. Seow J, Graham C, Merrick B, Acors S, Steel KJ, Hemmings O, *et al*. Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection. MedRxiv 2020. Doi: https://doi.org/10.1101/2020.07.09.20148429.
8. Xiang F, Wang X, He X, Peng Z, Yang B, Zhang J, *et al*. Antibody detection and dynamic characteristics in patients with COVID-19. Clin Infect Dis 2020:ciaa461.
9. Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, *et al*. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. MedRxiv 2020. doi: https://doi.org/10.1101/2020.03.30.20047365.
10. Lin Q, Zhu L, Ni Z, Meng H, You L. Duration of serum neutralizing antibodies for SARS-CoV-2: Lessons from SARS-CoV infection J Microbiol Immunol Infect 2020;53: 821-2.
11. Long Q, Tang X, Shi Q, Li Q, Deng HJ, Yuan J, *et al*. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med 2020;26:1200-4.
12. Callaway E, Ledford H, Mallapaty S. Six months of coronavirus: The mysteries scientists are still racing to solve. Nature 2020;583:178-9.
13. Sekine T, Perez-Potti A, Rivera-Ballesteros O, Strålin K, Gorin JB, Olsson A, *et al*. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. Cell 2020;183:158-68.
14. Ni L, Ye F, Cheng ML, Feng Y, Deng YQ, Zhao H, *et al*. Detection of SARS-CoV-2-specific humoral and cellular immunity in COVID-19 convalescent individuals. Immunity 2020;52:971-7.e3.
15. Rajendran K, Krishnasamy N, Rangarajan J, Rathinam J, Natarajan M, Ramachandran A. Convalescent plasma transfusion for the treatment of COVID-19: Systematic review. J Med Virol 2020;92:25961.
16. Rao V, Kannan S, Kumar J, Arakeri G, Subash A, Batra HV, *et al*. COVID-19: An insight into the developments in diagnostics and therapeutics in India. Indian J Med Sci 2020;72:77-82.
17. Mascarenhas A. Plasma Therapy may not Reduce Mortality, Suggests ICMR Study; 2020. Available from: https://www.

indianexpress.com/article/india/coronavirus-plasma-therapy-may-not-reduce-mortality-suggests-icmr-study-6589853. [Last accessed on 2020 Sep 15].
18. Guarner J. Three emerging coronaviruses in two decades. Am J Clin Pathol 2020;153:420-1.
19. Edridge A, Kaczorowska J, Hoste A, Bakker M, Klein M, Jebbink MF, *et al*. Coronavirus protective immunity is short-lasting. MedRxiv 2020; doi: https://doi.org/10.1101/2020.05.11.20086439.
20. Kumar S, Nyodu R, Maurya VK, Saxena SK. Host immune response and immunobiology of human sars-CoV-2 infection. In: Coronavirus Disease 2019 (COVID-19). Singapore: Springer; 2020. p. 43-53.
21. de Alwis R, Chen S, Gan ES, Ooi EE. Impact of immune enhancement on Covid-19 polyclonal hyperimmune globulin therapy and vaccine development. EBioMedicine 2020;55:102768.

How to cite this article: Rao V, Kannan S, Subhash A, Arakeri G, Gulia A. Current challenges and controversies surrounding SARS-CoV-2 immunity and their implications on reinfection, plasma therapy treatment outcomes, and vaccine development. Indian J Med Sci 2021;73(2):174-8.