HUMORAL IMMUNITY IN PATIENTS WITH SARS-COV-2 INFECTION: A REVIEW

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ABSTRACT

The COVID-19 pandemic caused by SARS-CoV-2 started in China in December, 2019 and has spread across several continents. As at 5th December, 2020, there have been 65,257,767 confirmed cases of COVID-19 worldwide with 1,513,179 deaths (2.31% mortality)

Humoral immune responses are highly specific and they provide long-lasting protection against reinfection and the titre of antibodies that persist is directly related to the extent of protection afforded. As research towards generating effective vaccines against SARS-CoV-2 are in advanced stages, there is need for continued robust review of the available data from various studies on the antibody response from natural SARS-COV-2 infection as regards the potential for immunity against re-infection following exposure to the antigens of this virus. Antibodies against RBD of the spike protein of SARS-CoV-2 were detected in majority of patients, appearing within the first week, peaking by 3rd week. IgG antibodies was observed to last beyond 120days and it is predicted seroreversion would happen at about 42.72 months.

Antibody response to SARS-CoV-2 correlates with the severity of COVID-19. It was also higher amongst males, hospitalized patients, older people and patients with higher BMI and was lower among smokers, immunosuppressed individuals and patients using anti-inflammatory medications.

Persistence of high levels of antiSARS-CoV-2 neutralizing antibodies (IgG) following natural infection is thus likely to be associated with conferment of long term protection against re-infection or attenuate disease severity if reinfection occurs. There is a good potential for development of immunity against SARS-CoV-2 infection in vaccinated individuals.

Keywords: SARS-CoV-2, Antibody response, AntiSARS-CoV-2 antibody

INTRODUCTION

The COVID-19 pandemic caused by SARS-CoV-2 started in Hubei province, China in December, 2019 and has spread across all continents except the Antarctica. Globally, as of 5 December 2020, there have been 65,257,767 confirmed cases of COVID19, including 1,513,179 deaths. (2.31 %).[1]

Adaptive immune response involves T cells, which seek out and destroy cells that have been infected by the invading pathogen (cell mediated immunity) and B cells the produce antibodies targeted against particular disease causing organisms (humoral).

IgM antibodies are produced first and disappear after a few weeks and their presence as such suggest recent infection. IgG antibodies are produced at the same time or 2-3 days later, and titres (levels) usually remain for months or years, their co-existence with IgM antibody suggest recent infection and when they occur alone, it denotes prior infection[2] and their persistence suggests development of immunity.[3]

Humoral immune responses are highly specific and they provide long-lasting protection against reinfection. The quantity of antibodies that persist is directly related to the extent of protection afforded against the virus that induced them.[4]

Antibodies act by either prevention infection of cells by binding to the virus and preventing its interaction with its receptor (neutralizing antibodies) or by causing destruction of infected cells and virus bound to them and marking them for demolition through cell mediated immune response (binding antibodies)

Neutralizing antibodies play a major role in viral clearance and prevention of re-infection and their continued presence in the apparent absence of the

inducing pathogen backed up by memory cells provides a first line of defense against re-infection.[3,5] Consequently, they are central to reducing transmission of infection as well as limiting morbidity and mortality from infections. Thus in epidemics and pandemics, like COVID-19, ability to generate adequate and lasting neutralizing antibodies against viral infection is essential for its limiting viral spread.[6]

Researches towards generating effective vaccines that protect against SARS-CoV-2 infection are in advanced stages, however, there is limited understanding of the antibody response from natural SARS-COV-2 infection. There are concerns that SARS-CoV-2 infection may induce transient antibody response[4] raising apprehension about risk of re-infection and the uncertainty about the duration of vaccine protection.[7] A proper understanding of antibody response to SARS-CoV-2 will help guide development of modalities and strategies for vaccination.[7,8]

OBJECTIVES

This review aims to:

1. Profile the antibody response among individuals who are infected with or have recovered from SARS-CoV-2 infection, viz a viz:
   - the occurrence of antiSARS-COV-2 antibodies
   - longevity of antiSARS-COV-2 antibodies
   - factors that determine the magnitude of the antibody response
2. Find possible evidence of protection against SARS-CoV-2 infection/re-infection from the immune response to natural exposure to the virus/ viral antigen.

METHOD OF THE REVIEW

Google, Google scholar, Pubmed, Ajol were searched over a 2 week period (between 23rd of November 2020 and 6th December 2020) for articles with data of studies on the antibody response to SARS-CoV-2 using the following search terms: immune response against SARS-CoV-2, antibody response to SARS-CoV-2, antiSARS-CoV-2 antibodies, antibodies against SARS-CoV2 Spike/S protein, anti-SARS-CoV-2 RBD antibodies, immunity against SARS-CoV-2 re-infection, anti-SARSCoV-2 neutralizing antibodies.

From the result of the searches done above, a total of 30 studies were selected for this review. Information as to the presence of anti-SARS-Cov-2 antibodies, the time of appearance of these antibodies, the time of peaking of antibody titre, time of commencement of antibody decay, time to seroreversion were abstracted from these papers where available.

Information about the group of patients with the highest and lowest antibody titres as well as reports of re-infection following recovery were also obtained where available.

RESULTS OF THE REVIEW

CoronaVirus Antigen and Antibody Response

Neutralizing antibodies are usually generated against antigens on the membrane of the infective agent. Antibodies to SARS-CoV-2 can target any of its antigens, the receptor binding domain (RBD) on the spike protein on the membrane of SARS-CoV-2 is the commonest target for antibody assays.[9]

The spike protein on SARS-CoV-2 is a glycoprotein that contains the receptor binding domain (RBD), this is used by the virus to attach to the receptor (angiotensin converting enzyme 2 (ACE2) receptor) on the surface of the mucosa of the host cell.[9,10,11]

Neutralization antibody titers which play a key role in viral clearance and protection against infection have been found to significantly correlate with anti-spike titres (titers against RBD),[5,9, 12] especially IgG titres.[6] This was also observed by Lou *et al.* who noted decline in viral load with increasing antibody levels.[13]

Furthermore, levels of neutralizing antibody titres have also being found to correlate to numbers of virusspecific T cells.[14]

This suggests that IgG antibody titres could be used to speculate the overall adaptive immune response against SARS-CoV-2 infection and the attendant protection from infection/re-infection.

TIME OF APPEARANCE OF ANTI-SARSCoV-2 ANTIBODIES

IgM antibodies against SARS-CoV-2 can be present within the first few days (by day 3 after infection), with IgG counterparts appearing a few days later.[15,16] seroconversion for all (IgM, IgG, NAb) antibodies was observed for most patients to have occurred by second to third week post infection[7,8,15,16,17] Expectedly, IgM antibodies appeared earlier and peaked faster than IgG anti SARS-CoV-2 antibodies.[17,18] However, the time to seroconversion in asymptomatic and mild COVID-19 cases was longer.[9] Anti-SARS-CoV-2 S-specific, IgM antibodies peaked at days 2025days from onset of symptoms.[7,18,19,20]

Anti-SARS-CoV-2 S-specific IgG antibodies were identifiable from day 7 onwards and peaked in the 4th -5th week (day 25-35).[7,18,19,20] Some studies also found that all patients develop IgG antibodies by 19-

20 days after infection.[5,21]

DURATION OF SARS COV 2 ANTIBODIES

The neutralizing antibody titre is made up in the early phase of the disease by IgM antibodies, however as IgM antibodies decay, anti-SARS-CoV-2 neutralizing antibodies are majorly comprised of its IgG forms. This transition could take six weeks to occur.[7]

Antibody titres for IgM start to decline after peaking,[18,19] with estimated half-life of 10.36 days[7] leading to significant reduction in serum titres noted by 4th week after onset of illness.[19] Estimated duration to seroreversion for anti-SARS-CoV-2 IgM could be between two and a half months[18,20] and four and half months[7] after the onset of illness.

There are reports of waning of anti-SARS-CoV-2 IgG antibodies but at a much slower rate than IgM and sero-reversion was not seen to be common among COVID-19 survivors.[18] Several studies report antiSARS-CoV-2 IgG antibodies persisting at high levels beyond 53 days,[5] 90 days,[4,18] and 120 days[19,22]from the time of infection. Estimated half-life of anti-SARSCoV-2 IgG antibodies is 177.39 days,[7] and it is projected that it will take about three and half years (42.72 months) for sero-reversion for anti-SARS-CoV2 IgG.[7]

These findings suggests that humoral immunity against SARS-CoV-2 acquired by natural infection may remain present for a while and may confer protection against re-infection.

However, Long *et al.* in a study comparing antibody response between asymptomatic and symptomatic individuals found some reduction in antiSARS-CoV2 IgG and neutralizing antibody levels after about 2 months from time of discharge, by which time, 40% and 12.9% of asymptomatic and symptomatic individuals respectively in their study had become seronegative for antiSARS-CoV-2 IgG.[17]

FACTORS AFFECTING SARS COV 2 ANTIBODIES

Review from several studies have shown that the magnitude of antibody response to SARS-CoV-2 infection is directly related with severity of the symptoms of COVID-19[15-20,23-25] with patients who had asymptomatic or mild SARS-CoV-2 infection developing least quantities of antibody titres and patients requiring ICU admission, oxygen support having the highest titres.[5,18,21,26]

AntiSARS-CoV-2 antibody titres was also found to be higher in older patients[5,12,20,22] probably because they are more likely to have severe disease from SARSCoV-2 infection.

Hospitalized persons were also found to develop detectable antibodies faster and to higher levels than non-hospitalized persons[12,22] Symptomatic patients are more likely to need hospital admission and the more severe the symptoms the higher the antibody response.[22] Furthermore, of the symptoms of COVID-19, fever and breathlessness requiring oxygen support were independently associated with higher neutralizing antibody titre.[8]

Kae *et al.* in a review of antibody response in sera of COVID-19 patients, found neutralizing antibody in 100% of patients who presented with pneumonia, in 93.9% of patients with mild symptoms, and in 80.0% of asymptomatic patients.[27] this was corroborated by other studies who found that neutralizing antibody titer was higher and peaked faster among ICU patients than among non-ICU patients.[8,28]

Antibody response against SARS-CoV-2 was also noted to be enhanced in patients with higher BMI[22], perhaps because they are more likely to have comorbidities which predispose them to having severe disease from SARS-CoV-2 infection.

AntiSARS-CoV-2 antibody titre in infected patients was lower among smokers and patients using antiinflammatory medications[22] immunosuppressed patients.[18] Likely due to inability to mount immune response or factors suppressing immune response led to lower antibody response.

AntiSARS-CoV-2 antibody titre in infected patients was lower among females.[12,22] Though Xiaoli *et al.* did not find any significant difference in antibody titres in relation to gender from univariate and multivariate analysis.[5] However, from epidemiological studies males were more likely to have more severe disease from COVID-19 and thus, may have higher antibody titres than females.[29-32]

These findings suggest that prior infection with SARSCoV-2 should not be used to exclude people from vaccination especially those who had asymptomatic infection or mild disease, as well as the immunosuppressed patients, smokers and patients on long term anti-inflammatories. The requirement of booster doses should also be considered at earlier periods in this population.

PRESCENCE OF ANTIBODIES AND RISK OF REINFECTION

Clarity as to development of protection and duration of protection from SARS-CoV-2 re-infection following recovery from COVID-19 has not been ascertained.[9] However, previous studies following other human coronavirus (SARS-CoV, MERS-CoV) infection showed that neutralizing antibodies against these viruses can remain persistent at high levels for years and these provide protection from re-infection or reduce severity of disease, even if re-infection occurs.[9]

Persistence of high levels of antiSARS-CoV-2 neutralizing antibodies (IgG) following natural infection is thus likely to be associated with conferment on long term protection against re-infection[2,9,26,33] or attenuate disease severity if re-infection occurs[9] and could be associated with prevention of infection in vaccinated individuals.

Anti-SARS-CoV-2 IgG antibodies contribute to the long term neutralizing antibodies,[34] and as such IgG titres after recovery are more indicative of protection against re-infection or reduced disease severity following re-infection.

Lu *et al* in a study of involving 87 COVID-19 patients who were diagnosed with re-infection following recovery and discharge from hospital, noted that all patients who tested positive again for the infection were observed to have had mild or moderate disease at initial diagnosis and were younger.[35]Suggesting those who are likely to have reduced antibody response/ neutralizing antibodies might be at an increased risk of incomplete viral clearance and re-infection,[35] although infectivity of these residual viral particles in the host is not clear.[36]

CONCLUSION

We don't know for how long SARS-CoV-2 infection will be with us but we know we need curb its spread. Antibody response to the viral antigens of SARS-CoV2 will guide our vaccination strategies. There is evidence of robust antibody response in most patients who were infected with SARS-CoV-2 infection, the degree of which is correlated with severity of symptoms. Persistence of high levels of neutralizing (IgG) antibodies is likely to confer protection against reinfection or reduce severity of COVID-19 following re-infection.

RECOMMENDATION/PUBLIC HEALTH IMPORTANCE

1. The findings in this review highly suggest that vaccination against SARS-CoV-2 might provide long term protection against SARS-CoV-2 infection in majority of the population and as such should be made available to the populace as soon as feasible.
2. Previous infection with SARS-CoV-2 should not be used as an exclusion criteria for vaccination especially for patients who had asymptomatic or mild infection.
3. Booster doses might be required in selected situations.
4. There is need for further studies to quantify the antibody titre following vaccination against SARSCoV-2 and subsequently determine the appropriate interval for booster doses.

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