Review paper

COVID-19 humoral response

COVID-19 – odpowiedź humoralna

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Słowa kluczowe: SARS-CoV-2, przeciwciała neutralizujące, odpowiedź immunologiczna, leczenie COVID-19, sztorm cytokinowy.

Abstract

This article reviews studies on SARS-CoV-2 antibodies, including neutralizing antibodies (NAbs) and post-vaccination response. The SARS-CoV-2 virus is closely related to SARS-CoV and MERS-CoV, sharing 79% and 50% of its genome sequence with them, respectively. Antibodies are crucial in identifying and destroying pathogens such as viruses, and understanding virus-specific antibodies can help end pandemics quickly. The SARS-CoV-2 virus uses the spike protein to enter human cells via the angiotensin-converting enzyme 2 receptor (ACE2). The immune response to the virus involves various components, including dendritic cells, T cells, B cells, and NAbs. Seroconversion, antibody kinetics, and immune response after COVID-19 vaccination are essential factors in understanding the virus and developing treatments. Neutralizing antibody therapies have been explored as potential treatments, but the emergence of viral variants challenges their long-term development. Lessons learned from antibody-based therapies can influence future strategies for treating emerging infectious diseases.

Streszczenie

Niniejszy artykuł jest przeglądem dotychczasowych badań dotyczących odpowiedzi humoralnej przeciwko COVID-19, ze szczególnym uwzględnieniem przeciwciał neutralizujących (NAbs). Wirus SARS-CoV-2 jest blisko spokrewniony z wirusami SARS-CoV i MERS-CoV, dzieląc z nimi odpowiednio 79% i 50% sekwencji genomu. Przeciwciała odgrywają kluczową rolę w identyfikowaniu i niszczeniu patogenów, takich jak wirusy, a zrozumienie przeciwciał specyficznych dla wirusa może przyspieszyć zakończenie pandemii. Wirus SARS-CoV-2 za pomocą białka kolca wnika do ludzkich komórek za pośrednictwem receptora enzymu konwertującego angiotensynę 2 (ACE2). Terapie oparte na przeciwciałach neutralizujących wraz z coraz nowszymi wariantami wirusa stają się coraz mniej skuteczne.

Introduction

The SARS-CoV-2 virus, which caused the COVID-19 pandemic, has been the subject of a vast number of studies around the world. In this article, we review current studies regarding SARS-CoV-2 antibodies, including neutralizing antibodies (NAbs) and post-vaccination response. According to Pekar *et al.* [1], the first human-to-human transmission took place in mid-October or mid-November 2019. The World Health Organization (WHO) announced a public health emergency of international concern on January 30, 2020 and the COVID-19 pandemic was declared on March 11, 2020. By July 2020, more than 300,000 people had died because of COVID-19 and the virus had spread around the world. We witnessed a very rapid reaction by the scientific community: by January 5, 2020, the Wuhan Institute of Virology had sequenced the whole virus genome [2], starting the large-scale race for a COVID-19 vaccine. This sequencing took place just one week after the first case, which was reported on December 31, 2019. The first COVID-19 human vaccine trials began in March 2020. After numerous studies, the BNT162b2 vaccine was finally allowed for commercial use on December 2, 2020 – initially by the United Kingdom's Medicines and Healthcare prod-

ucts Regulatory Agency (MHRA), and subsequently by other countries' regulatory agencies. More than one billion COVID-19 vaccine doses had been administered globally by April 2021.

The SARS-CoV-2 virus is closely related to two highly pathogenic coronaviruses: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). The novel coronavirus shares 79% of its genome sequence with SARS-CoV and 50% with MERS-CoV [3]. Despite their differences, these viruses have one thing in common: they have jumped the immunology barrier and started human-to-human transmission.

Antibodies (along with dendritic cells, T cells, and B cells) play a crucial role in communicating the presence of a pathogen to immune effector cells. An antibody, also known as immunoglobin (Ig), is a heavy, Y-shaped protein used to identify and destroy pathogens such as bacteria and viruses. Most antibodies are composed of four polypeptide chains – two copies of a heavy chain and two copies of a light chain – connected by disulfide bonds [4]. Moreover, an antibody is also separated into two antigen-binding fragments (FAB) contacting domains and forming a characteristic Y shape. The F_V region is the subregion of FAB that binds to an antigen. There are two identical antibody-binding sites on a single antigen, which allows it to bind strongly to a multivalent antigen and to form antibody complexes. This plays a crucial role in activating other parts of the immune system. Being aware of this virus's specific antibodies could facilitate efforts to end this and future pandemics quickly.

SARS-CoV-2 structure and mechanism of entry into cells

The SARS-CoV-2 virus is built of various proteins: membrane (M), envelope (E), nucleocapsid (N), and spike (S). The N protein holds the virus's RNA genome. Together, the E, S, and M proteins create the viral envelope. The mechanism of entry into human cells is closely related to the angiotensin-converting enzyme 2 receptor (ACE2) [5, 6]. Coronaviruses use the homotrimeric spike glycoprotein, which is divided into S1 and S2 subunits on the envelope, to bind to their receptors. SARS-CoV-2 enters human cells with the mediation of the spike protein, which is duplicated multiple times on the surface of the virus. The S1 subunit binds to the ACE2 receptor, while the S2 subunit binds to the cell membrane, initiating peptide-mediating membrane fusion. The mechanism of SARS-CoV-2 membrane fusion is very similar to that proposed for HIV membrane fusion [7]. At this stage, the first cellular immune mechanisms can be observed. Toll-like receptors (TLRs) are responsible for producing type I interferons once they recognize the virus [8]. Among these TLRs, TLR7 and TLR8 play a special role: they bind single-stranded viral RNA and induce pro-inflammatory cytokines. These two TLRs are expressed mostly in the lung, brain, skin, and lymphoid tissues.

Antibody response in COVID-19 patients

In the early stage of the pandemic, Zhang *et al.* were the first to establish a specific SARS-CoV-2 antibody detection test [9]. Moreover, they noted that a molecular diagnosis based on oral swabs detected only 50% of COVID-19 cases; in contrast, the serology test detected almost 100% of the positive cases. After infection, the S and N proteins are the main targets of the immune response. According to Sun *et al.*, the antibody response was more chaotic and less linear in ICU patients than in non-ICU patients [10]. N protein antibodies, unlike the S protein antibodies, are unable to neutralize the virus [11]. NAbs interact with other parts of the immune system, such as phagocytes or natural killer cells, facilitating effective neutralization of SARS-CoV-2. Apart from their protective function, these antibodies can induce a harmful antibody-dependent enhancement (ADE), which was observed in the previous SARS-COV pandemic. ADE is mediated by the Fc receptors (FcRs) found on many immune cells, such as monocytes, macrophages, and B cells [12]. Furthermore, during the SARS-CoV pandemic, ADE in macrophages led to elevated levels of tumor necrosis factor and IL-6 [13]. Another conclusion drawn from the SARS-CoV pandemic is the fact that antibodies targeting different S-protein epitopes have different potential to induce ADE. Antibodies targeted to the receptor-binding domain (RBD) or the H2 domain of the S protein induced a better antibody response in non-human primates, while antibodies targeting other S protein domains were related to a higher risk of ADE. Moreover, recent studies have found a correlation between antibody kinetics and disease severity. Rijkers *et al.* observed that patients with a severe form of the disease developed a robust antibody response to SARS-CoV-2, including IgG and IgA antibodies. Patients with mild symptoms experienced a modest antibody response [14]. Ren *et al.* also reported a clear link between the dynamics of antibody production and disease severity. A delayed antibody response was associated with a more severe course of the disease, in contrast to the earlier response characteristic of patients with a mild form of the disease [15].

Seroconversion and antibody kinetics

A longitudinal prospective study of 1000 patients conducted by Yadav *et al.* reported that the median time for seroconversion was 10 days for IgG and 8 days for IgM [16]. Severe cases of COVID-19 tended to have an earlier seroconversion than mild ones. According to other studies, the combination of SARS-CoV-2 IgG and IgM antibodies was observed in 75% of patients; IgM peaked in the second week of infection, while IgG

Table 1. Comparison of SARS-CoV-2 antigen tests [31–33]

Antibody test	Sensitivity	Specificity
ELISA – DiaSorin	90–97%	90%
Maglumi – nCoV CLIA	82–83%	88–93%
Biosynex BSS test	83–95%	88–75%
Abbott Panbio LFT test	72%	100%
PCL COVID-19 Ag FIA test	69.8%	94.1%

peaked in the third week [17]. This seroconversion rate differs from other studies, which reported values between 70% and 90%. This is most likely related to different laboratory methods. Zhang *et al*. found that among ICU patients, the seroconversion time for both IgG and IgM antibodies was up to one month [18]. According to Agarwal *et al*., there was no difference in seroconversion rate according to age, comorbidities, or treatment groups [19]. No correlation between antibody levels and sex was proven. The duration that antibodies are present among convalescents is a very important issue from a public health perspective. According to Hedges *et al*., 50% of subjects maintained a high level of neutralizing antibodies for at least 6 months. The participants with the highest starting titers had the longest-lasting response, up to 12 months after the diagnosis. In this group, the antibody response after SARS-CoV-2 vaccination was much higher and lasted longer than in the convalescent patients [20]. Achiron *et al*. reported that a protective level of NAbs lasted at least 9 months in a group of convalescents [21]. According to most studies, anti-spike protein and anti-RBD antibodies showed the highest neutralizing potential [22]. The available data indicate that NAbs are produced by many B cells with little or no affinity maturation required [23–25]. These data also suggest that SARS-CoV-2 NAbs are developed from naïve B cells instead of pre-existing cross-reactive memory B cells. Although there is no evidence of a correlation between age and NAb levels, Varona *et al*. observed that among patients older than 45 years, NAb levels were more stable than among younger patients [26].

COVID-19 antibody tests

The rapid spread of SARS-CoV-2 in society created an urgent need to develop fast diagnostic methods. Antibody tests seem to be a great alternative to expensive, time-consuming PCR methods. Even though antibody tests do not detect active disease, they do have some advantages over nucleic acid tests and antigen tests. First of all, they have a much longer detection window. Another advantage is the fact that the distribution of antibodies in the blood is more uniform than the viral load in respiratory samples, which may cause false negatives with PCR. Antibody tests may be applied in convalescent plasma donor research to determine the level of protection in patients with immune deficits, or it can simply be supplementary in the diagnosis of COVID-19. Currently, neutralization assays seem to be the standard method for these measurements. Moreover, the role of this test is to evaluate the diagnostic performance of binding antibody tests, which is the most popular antibody test method. Binding antibody tests have been developed to detect immunoglobins IgA, IgM, and IgG, including ELISA, ICG assay, electrochemiluminescence immunoassay (ECLIA), CLIA with enzyme or non-enzyme labels, fluorescence immunoassay (FIA), LFIA, protein microarrays, biosensors, and immunofluorescence assays (IFA) [27]. There are a few reasons for false positives, one of which is the cross-reactivity towards the SARS-CoV, MERS-CoV, HCoV-HKU1, HCoV-OC43, HCoV-229E, HCoV-Alpha1, dengue, and hepatitis B viruses [28–34] (Tables 1, 2).

Immune response after COVID-19 vaccination

According to the literature, the BNT162b2 vaccine induces a moderate level of anti-S1 IgA and IgM after two doses, though a strong IgG response was observed [35]. Wheeler *et al*. investigated the dynamics of the antibody response by comparing four vaccinations. The first dose of vaccination induced an immune response two weeks after injection. A second dose resulted in a 100-fold increase in antibodies in every

Table 2. Potential reasons for false results from COVID-19 NAb-based tests [34]

False positive test result	False negative test result
Autoantibodies: Endogenous antibodies that react with self-antigens or assay components may be present	Prozone phenomenon: High NAb titers can lead to the formation of antigen/antibody complexes that do not precipitate
Cross-reactivity: Antibodies targeting similar epitopes on different antigens may bind to the target antigen nonspecifically	Immunosuppression: Conditions such as AIDS or immunosuppressive therapies can impair the immune system's ability to produce detectable levels of NAbs
SARS-CoV-2 vaccination is IgG-positive long after an initial infection	Early test implementation: In the early stages of infection or post-vaccination, the immune system may not have generated sufficient NAbs to be detected
Exogenous factors: e.g., high concentrations of nasal spray, non-specific binding, or contamination	Exogenous factors e.g., sample degradation, or contamination

Table 3. Factors influencing the immune response to SARS-CoV-2 vaccination [46–51]

Age	Advanced age is associated with immunosenescence, a decline in immune system function that can result in a reduced ability to generate a robust immune response to vaccinations
Immunosuppression	Conditions such as HIV/AIDS or the use of immunosuppressive therapies can impair the immune system's capacity to mount an effective response to the vaccine
Genetic factors	Inter-individual genetic variability, particularly in genes related to immune system function, can influence the strength and duration of the immune response to vaccination
Nutritional status	Malnutrition, micronutrient deficiencies, or an imbalance in essential nutrients can compromise immune system function and affect the response to vaccination
Comorbidities	Certain underlying medical conditions, such as diabetes, chronic kidney disease, or autoimmune disorders, can impair immune function and affect vaccine response
Prior SARS-CoV-2 infection	The presence of pre-existing immunity due to previous SARS-CoV-2 infection may impact the immune response to COVID-19 vaccination, increasing the response

group, including the patients who had not responded after the first dose. Their antibody levels were significantly higher than those of the convalescent group. According to Martinez-Baz *et al.*, the incidence of symptomatic COVID-19 infection was three times lower in the patients vaccinated with the second dose vs. patients vaccinated only once (15.5% vs. 5.1%) [36]. Interestingly, RBD and S1 antibody levels were much higher after the second dose than any levels after the first dose. This could mean that the first dose of vaccination could induce an immunologic response, even among patients who exhibited no increase in antibodies after the first vaccination. According to Ibarrondo *et al.*, a sharp increase in antibodies was observed in convalescents after the first dose, but there was no further rise after the second one [37]. Tada *et al.* observed lower seroconversion related to SARS-CoV-2 vaccination during anti-CD20 monoclonal antibody and fingolimod therapy in a group of patients with multiple sclerosis [38]. A weaker post-vaccination immunologic response was also observed in a group of patients with active cancer [39]. Moreover, it was also observed that the dynamics of falling antibody levels was similar in convalescents and vaccine recipients, with a 90% loss within 90 days [40].

Tada *et al.* compared NAb titers after vaccination with the mRNA vaccines BNT162b2 and mRNA-1273 versus adenoviral vector-based single-dose Ad26.COV2.S vaccination. The study reported much higher neutralization titers in the mRNA-based vaccines [38]. However, some recent studies have demonstrated that combining ChAdOx1nCoV-19 adenoviral vector vaccine with the previous BNT162b2 proved to be effective against the new variants of concern [40–43].

An important question is how the new variants of the virus affect the ability to produce specific NAbs. Muik *et al.* found that after two doses of BNT162b2 vaccine, Omicron-neutralizing titers were reduced 22-fold compared to the primary version of SARS-CoV-2 [41]. The level of NAbs significantly increased one month after a third dose of vaccination. This could mean that there is a need for a third dose, as well as for vaccines adapted to newer variants of this coronavirus. Khoury *et al.* reported that the neutralization level required for 50% protection against detectable SARS-CoV-2 was 20.2% of the mean convalescent level in seven different cohorts [42]. Larger decreases in NAb titers were reported among younger patients, those previously vaccinated against influenza and those with no previous COVID-19 infection [44–51] (Table 3).

Neutralizing antibody therapies for COVID-19

The COVID-19 pandemic has compelled society to explore new technologies to treat active infections. Drugs based on neutralizing antibodies appear to be a promising avenue. The first antibody-based drug granted emergency use authorization (EUA) in the USA was tixagevimab/cilgavimab, a combination of monoclonal antibodies administered via intramuscular injection for pre-exposure prophylaxis. In the group of patients receiving this treatment, a lower mortality rate was observed (9% compared to 12% in the placebo group). However, in February 2023, the FDA revoked the authorization due to its inefficacy against the XBB.1.5 subvariant [52]. A phase 3 study of casirivimab/imdevimab reported a 70% reduction in hospitalizations when administered at a daily dose of 1200 mg and a median duration of symptoms that was four days shorter. Despite these findings, the WHO advised against the use of casirivimab/imdevimab in the 13th version of the COVID-19 Therapeutic Guidelines, released on January 13, 2023 [53].

The most significant challenge for neutralizing antibody therapies in treating COVID-19 patients is the emergence of viral variants. The increased resistance of new SARS-CoV-2 variants, such as Omicron, to neutralizing antibodies limits the long-term development of this treatment approach. A potential solution could involve targeting conserved sites less likely to mutate. Zhou *et al.* reported that targeting

the S2 stem-helix fusion region of the spike protein yielded comparable effectiveness while reducing the risk of mutation at this epitope [54]. Our experience treating COVID-19 with neutralizing antibodies provides valuable insight that may be highly applicable in addressing the inevitable future pandemics. The lessons learned from developing and implementing antibody-based therapies can inform and expedite the creation of effective treatments for emerging infectious diseases.

Pathological antibody response

Although the humoral response is aimed at combating the SARS-CoV-2 virus, unwanted reactions have also been observed. It has long been known that NAbs activate specific immune complexes, leading to cytokine storm [55]. Recent studies have demonstrated that an IgG-specific immune complex was detected in the vascular walls of the lungs in 6 severe cases [56]. These specific IgG complexes are associated with acute respiratory distress syndrome in the most severe cases. Some publications have reported incorrect glycosylation in the Fc region of S1/S2 IgG antibodies in critical patients [57, 58]. This incorrect glycosylation in immune complexes can lead to the excitation of macrophages with FcγRIIIa or FcγRIIa, which in turn can lead to cytokine storm and the secretion of cytokines such as IL-6 or tumor necrosis factor. Another unwanted effect caused by IgG-specific immune complexes is platelet-mediated thrombosis [59]. According to Bastard *et al.*, at the onset of critical disease, 101 of 987 patients with life-threatening COVID-19 pneumonia had neutralizing IgG autoantibodies against interferon-w (13 patients), against the 13 types of IFN-a (36 patients), or against both (52 patients) [59]. For comparison, those autoantibodies were detected in only 4 out of 1227 healthy individuals. Other studies have also reported that autoantibodies against immunomodulatory proteins such as cytokines, chemokines, and cell-surface proteins have been observed in severe COVID-19 patients. This may indicate a significant role for the proteins in critical COVID-19 pathogenesis. Membrane attack complexes have been found in the liver, kidney, hearts, and lungs of patients with severe disease. SARS-CoV-2 can induce the complement activation pathway in a few ways: classical, lectin, and alternative pathways. Higher levels of IgG1 and IgG3 were found, as were higher levels of the activated complement components C3a, C3b, C4b, and C5a. This concentration of the complement activation pathway was related to disease severity [60].

Conclusions

The humoral response against SARS-CoV-2 presented in this article is just a part of the immune response, which includes cell-mediated immunity and the innate immune system. Our knowledge about this pathogen is growing every day. On the other hand, its ability to mutate rapidly is a serious global public health threat. We still need additional studies, as this knowledge may be crucial in future global pandemics as well.

Conflict of interest

The authors declare no conflict of interest.

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