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Review Article

Monoclonal antibodies: their place in applied medicine and their role in the newest infectious disease – history, present, and future. Literature review

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Abstract

Monoclonal antibodies (mAbs) are immunoglobulins with practically absolute specificity (monospecificity) for a particular antigen (epitope). Over the past three decades, monoclonal antibodies have undergone a remarkable transformation, evolving from their use predominantly as research tools to becoming increasingly powerful therapeutic agents in medical practice. Personalized therapy and targeted treatment of diseases form the cornerstone of modern medicine's revolutionary capabilities. Monoclonal antibodies are a shining example of personalized therapy, developed based on deep and continuously growing knowledge in the fields of immunology, molecular biology, and biochemistry. The accepted nomenclature for monoclonal antibody names indicates their origin: murine (-omab), chimeric (-ximab), humanized (-zumab), or recombinant (-umab). Monoclonal antibodies belong to the IgG class. Monoclonal antibodies of this class possess specific properties and advantages. They are characterized by optimal pharmacokinetics, stability, and low immunogenicity (especially recombinant forms), a low toxicity profile, and the capacity for large-scale production of specific monoclonal antibodies targeting diverse antigens. The mechanisms of action of monoclonal antibodies include direct cell toxicity, immune-mediated cell destruction, vascular destruction, and immunomodulatory functions. The pathophysiology of many conditions treated with monoclonal antibodies is equally intricate, involving numerous cells and molecules. Monoclonal antibodies, in general, are characterized by good tolerance. The scientific community continues its efforts to enhance their efficacy, reduce their immunogenicity, and optimize their pharmacokinetic properties, as well as attempts to achieve oral (mucosal) bioavailability. The use of monoclonal antibodies in modern medicine is continuously expanding, with their incorporation into therapeutic regimens for numerous severe non-malignant diseases such as asthma, atopic dermatitis, migraine, hypercholesterolemia, osteoporosis, bacterial infections (e.g., anthrax), and viral infections (such as COVID-19). Efforts are being directed not only at improving the structural and functional properties of existing monoclonal antibodies but also at creating new types of antibodies with smaller molecular weights and higher specificity. As a next

generation of nanobiotechnology, natural and synthetic nanobodies have been utilized in numerous fields of biomedicine, including as biomolecular materials, for various biological studies, and in medical diagnostics and immunotherapy. Monoclonal antibodies and antibody-based molecules offer a reliable opportunity to effectively counter emerging viral pathogens and antibiotic-resistant bacteria. When administered to patients with a healthy immune system, they can provide necessary prophylaxis against specific diseases, acting as vaccine-like molecules and promoting long-term, antimicrobial-specific immune responses. Monoclonal antibodies have been identified as a potentially effective therapy for preventing the progression of COVID-19 in patients at high risk of developing severe disease.

Keywords

monoclonal antibodies, COVID-19 infection, therapeutic agents, antibody-based molecules, biological products, pharmacokinetics, pharmacodynamics, specificity, efficacy, immunogenicity

History of monoclonal antibodies and their path through modern medicine

Monoclonal antibodies (mAbs) are immunoglobulins with practically absolute specificity (monospecificity) for a particular antigen (epitope) (LiverTox 2012). Over the past three decades, monoclonal antibodies have undergone a remarkable transformation, evolving from their use predominantly as research tools to becoming increasingly powerful therapeutic agents in medical practice (Singh et al. 2018). Personalized therapy and targeted treatment of diseases form the cornerstone of modern medicine's revolutionary capabilities. Monoclonal antibodies are a shining example of personalized therapy, developed based on deep and continuously growing knowledge in the fields of immunology, molecular biology, and biochemistry (Malik and Ghatol 2025).

The earliest documented (indirect) antibody-based therapy dates back to 1796, when Dr. Edward Jenner inoculated pustular material from smallpox lesions into a recipient to induce immunity. This not only marked Jenner as the father of immunology but also laid the foundation for the principles of vaccination. However, the use of monoclonal antibodies in humans was not established until 1975, when Köhler and Milstein conducted their pioneering work (Bayer 2019). The concept of using monoclonal antibodies as therapeutic agents is rooted in the functions of the immune system, particularly the humoral immune response—the synthesis of specific antibodies in response to encountering foreign antigens (Tiller and Tessier 2015). Antibodies produced as part of this immune response are proteins with high specificity and affinity for the specific antigen or molecule that triggered their generation.

Köhler and Milstein utilized these fundamental immunological principles to create the so-called "hybridoma" (a cell resulting from the fusion of myeloma cells and spleen-derived B-lymphocytes from mice) (Posner et al. 2019). The hybrid cells thus generated enabled the production of a particular clone of antibodies with selective specificity in large quantities— referred to as monoclonal antibodies. However, the early biotechnology for producing these "primitive" monoclonal antibodies soon encountered a critical limitation: the inability to use these antibodies for long-term therapy due to their immunogenicity and the rapid development of human anti-murine antibodies (HAMA). In addition to rapid clearance due to HAMA, subsequent applications of monoclonal antibodies could induce IgE production, leading to anaphylactic reactions in patients (Castelli et al. 2019).

Despite the challenges associated with the murine origin of the first monoclonal antibodies, research continued, leading to the development of alternative production methods that overcame these limitations. Chimeric clones represented the next step, where murine Fc regions were replaced with human Fc regions obtained through crystallization (Shepard et al. 2017). Examples of chimeric monoclonal antibodies include Infliximab and Rituximab.

Chimeric clones were followed by the development of "humanized" mAbs, where murine protein loops (acting as ligand-binding domains) were implanted into human immunoglobulins. Examples of monoclonal antibodies in this category include daclizumab and trastuzumab. The culmination of continuous advancements in monoclonal antibody production was the refinement of recombinant mAbs, which are identical to human-derived monoclonal antibodies. Recombinant mAb technology minimizes the risks associated with earlier versions. The accepted nomenclature for monoclonal antibody names indicates their origin: murine (-omab), chimeric (-ximab), humanized (-zumab), or recombinant (-umab) (LiverTox 2012).

The mechanisms of action of monoclonal antibodies

There are five classes of antibodies classified based on the type of heavy chains they contain: immunoglobulins IgM, IgD, IgG, IgE, and IgA (Tiller and Tessier 2015). Each class performs a specific, highly specialized function in the human body. The largest proportion belongs to IgG immunoglobulins. This class is further subdivided into four subclasses based on structural characteristics (location and quantity of disulfide bonds). Monoclonal antibodies belong to the IgG class (Buss et al. 2012). Monoclonal antibodies of this class possess specific properties and advantages. They are characterized by optimal pharmacokinetics,

stability, and low immunogenicity (especially recombinant forms), a low toxicity profile, and the capacity for large-scale production of specific monoclonal antibodies targeting diverse antigens. Complementarity-determining regions (CDRs) located in the antigen-binding fragment (Fab) of a particular antibody play a crucial role in determining specificity and affinity for the target epitope. This selectivity limits effects on other cells and systems. The Fc fragment, another specific region of the antibody, consists of constant domains and has the ability to activate the immune system against the antigen targeted by the monoclonal antibody. These complex functions are mediated through interactions with Fc receptors expressed on various endogenous cells and the complement system, triggering effector cascades targeting the monoclonal antibody's antigen (Castelli et al. 2019; Malik and Ghatol 2025).

The mechanisms of action of monoclonal antibodies include direct cell toxicity, immune-mediated cell destruction, vascular destruction, and immunomodulatory functions. Immune-mediated cell destruction encompasses complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), and antibody-dependent cellular cytotoxicity (ADCC). These mechanisms are triggered when Fc receptors expressed on endogenous cells (NK cells, macrophages) are activated via binding to the Fc regions of monoclonal antibodies. The human immune system operates through complex interactions among a variety of cells and molecules of both innate and adaptive immune responses (T cells, B cells, APCs, cytokines), ensuring comprehensive immunity and providing numerous opportunities for immunoregulation. The pathophysiology of many conditions treated with monoclonal antibodies is equally intricate, involving numerous cells and molecules (Krishnamurthy and Jimeno 2018; Shim 2020). In this context, the idea of bispecific monoclonal antibodies (bsmAbs) emerges, wherein targeting multiple pathophysiological mechanisms could enhance the efficacy of antibody-based biological therapy (Krishnamurthy and Jimeno 2018; Labrijn 2019). The main directions described in the literature for the development of bispecific monoclonal antibodies include inhibition of multiple cell surface receptors, blockade of multiple ligands, receptor cross-linking, and restoration of Fc receptors on T cells lacking such receptors (under normal conditions, these cells would not be activated through antibody stimulation due to the absence of Fc receptors). Despite the excellent theoretical possibilities and advantages of such a class of antibodies, their design, production, and use remain a challenge for the scientific community (Malik and Ghatol 2025).

Pharmacokinetics, pharmacodynamics, and adverse reactions

Monoclonal antibodies, in general, are characterized by good tolerance. Due to the fact that they are structurally large proteins (usually around 150–200,000 Daltons in size), they require parenteral, most commonly intravenous, administration (LiverTox 2012). The earliest created monoclonal antibodies were primarily directed against soluble cytokines, but the functions of modern therapeutic agents have also expanded to include their interaction with membrane-bound receptors. This has led to an increase in their circulating plasma half-life, which overall results in more complex pharmacokinetics and pharmacodynamics.

The basic principles of pharmacology applicable in the production of monoclonal antibodies have made it possible to generate these small molecules with high affinity, great potential, and selectivity, while minimizing their side effects and drug interactions. Due to the specificity of their strictly defined targeted action, monoclonal antibodies are characterized by increased therapeutic efficacy. The scientific community continues its efforts to enhance their efficacy, reduce their immunogenicity, and optimize their pharmacokinetic properties, as well as attempts to achieve oral (mucosal) bioavailability (Castelli et al. 2019).

Monoclonal antibodies, by nature, are proteins designed to closely resemble the structure of naturally produced human proteins in the body, thus ensuring a metabolism similar to theirs (they are not metabolized "typically" like other biologically inorganic and/or organic drugs).

A system exists that classifies the adverse reactions associated with the use of monoclonal antibodies, as described by Pichler et al. (2006) and Demlova et al. (2016). According to the mentioned classification, alpha-type reactions include symptoms associated with the syndrome of high-dose cytokine release into the systemic circulation. Beta-type reactions are those of an allergic nature, which can be mediated by IgG, IgE, or T-cells (either sudden or delayed in onset). Gamma-type reactions are due to immune imbalance syndromes, which may lead to autoimmune manifestations, allergic/atopic disorders, or damage to the immune system. Delta-type reactions describe manifestations of cross-reactivity that could occur when target antigens are expressed on other cells or structures. Epsilon-type reactions are associated with non-immunological adverse effects (Demlova et al. 2016; Malik and Ghatol 2025).

Despite advancements in the production of monoclonal antibodies and the significant reduction in immunogenicity of modern therapeutic classes, the described adverse reactions remain possible. The administration of monoclonal antibodies entails risks specific to biological products. This unique class of medications is characterized by numerous additional specifics in their use, requiring a thorough understanding of monoclonal antibodies and their mechanisms of action. For instance, the use of tumor necrosis factor (TNF) inhibitors, such as Adalimumab, necessitates a comprehensive medical history and meticulous assessment for potential latent tuberculosis. Since the specific inflammation in the human body (granulomas) caused by tuberculosis infection contains the pathogen, and the host's immune response is regulated by TNF signaling, suppression of this "TNF signaling" is contraindicated. Iatrogenic TNF inhibition resulting from monoclonal antibody administration may lead to

reactivation of latent infection. By a similar mechanism, suppression of the patient's immune system diminishes protective defenses, increasing predisposition to opportunistic and atypical infections (including fungal infections) and even the development of sepsis. These potential complications highlight the need for physicians working with monoclonal antibodies to possess comprehensive knowledge and preparedness to manage the specific adverse reactions associated with their use.

Anaphylaxis is a sudden hypersensitivity reaction (type I allergic reaction) that may also occur with the use of monoclonal antibodies. The anaphylactic reaction is mediated by the development of IgE antibodies against the monoclonal antibodies and is generally not expected to appear during the recipient's first exposure to any monoclonal antibody. However, cases of IgE cross-reactivity and the development of an anaphylactic reaction upon initial administration have been reported. According to the aforementioned classification, anaphylaxis is categorized as a beta-type reaction (Pichler et al. 2006). As with any other medication, monoclonal antibodies may also cause specific adverse reactions directly related to the mechanism of action of the respective monoclonal antibody (type A reactions). An example of such a reaction is the use of the monoclonal antibody Abciximab (a monoclonal antibody targeting glycoprotein GPIIb/IIIa) in patients undergoing percutaneous coronary intervention (PCI), which can lead to major hemorrhagic events (Vergara-Jimenez and Tricoci 2010).

The therapeutic spectrum of monoclonal antibodies

Monoclonal antibodies are widely used in both clinical and experimental medical practice. Many of the initial monoclonal antibodies employed in clinical settings primarily serve as immunomodulatory agents, targeting specific immune cells such as CD4 or CD3 lymphocytes, which play a critical role in the pathogenesis of rejection reactions following organ transplantation. Subsequently, monoclonal antibodies have been developed to act primarily against specific cytokines (anti-cytokine monoclonal antibodies) that are known to play a significant role in the cellular and tissue damage characteristic of autoimmune diseases, particularly rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel diseases, multiple sclerosis, and psoriasis. Additionally, the therapeutic spectrum of monoclonal antibodies has been expanded by leveraging their blocking or inhibitory activity against certain enzymes, cellular transport proteins, or signaling molecules that play key roles in the pathogenesis of oncological diseases as well as in the development of severe viral infections.

The use of monoclonal antibodies in modern medicine is continuously expanding, with their incorporation into therapeutic regimens for numerous severe non-malignant diseases such as asthma, atopic dermatitis, migraine, hypercholesterolemia, osteoporosis, bacterial infections (e.g., anthrax), and viral infections (such as COVID-19). As a result, monoclonal antibodies cannot be classified within a single nosologically defined class of therapeutic medications but instead have broad applications across various fields of clinical medicine.

Monoclonal antibodies have been approved for the treatment of cardiovascular, respiratory, hematologic, and nephrologic diseases, as well as for various conditions in immunology and oncology. Additionally, monoclonal antibodies are utilized in the treatment of several rare diseases and have specific indications, such as in the case of paroxysmal nocturnal hemoglobinuria. Furthermore, millions of patients with breast cancer, multiple sclerosis, rheumatoid arthritis, and other conditions have been successfully treated with monoclonal antibodies (Singh et al. 2018).

Monoclonal antibodies and inflammatory diseases. The new types of antibodies

In 2022, more than 80 therapeutic monoclonal antibodies were approved for use in the United States (LiverTox 2012). The contribution of monoclonal antibodies to the treatment of inflammatory diseases, particularly rheumatoid arthritis and inflammatory bowel diseases, as well as in the field of oncology, has led to revolutionary changes in the management of these serious conditions. Monoclonal antibodies are exceptionally promising therapeutic agents with continuously expanding applications (Posner et al. 2019). The field of molecularly targeted medicine and the high specificity of antibodies toward particular antigens drive the ongoing development of new therapeutic agents. Efforts are being directed not only at improving the structural and functional properties of existing monoclonal antibodies but also at creating new types of antibodies with smaller molecular weights and higher specificity. However, the realization of these ambitious projects still faces several significant challenges. Most therapeutic monoclonal antibodies identified and synthesized to date exhibit near-absolute specificity for key structures of target antigens. On the other hand, proteins often contain hidden native structures that underlie their specific functions. In this context, the development of stereospecific monoclonal antibodies that recognize the conformational structures of corresponding antigens provides a remarkably novel, universal approach in

targeted therapy. Refining and expanding their use could fundamentally alter key aspects of therapeutic monoclonal antibody application (Tsumoto et al. 2019). The advancement of this therapeutic class does not stop here. For example, camelid-derived antibodies, known as nanobodies or VHH, are unique proteins with distinct therapeutic potential. In contrast to conventional antibodies, nanobodies are unique fragments consisting only of a single heavy-chain variable domain, lacking light chains and the first constant domain (CH1). With a molecular weight as small as 12~15 kDa, nanobodies exhibit

the same antigen-binding affinity as conventional antibodies but with greater solubility. This feature gives them an advantage in recognizing and binding to functional, universal, target-specific antigenic fragments. Over recent decades, nano-MAbs have emerged as promising therapeutic agents and alternatives to traditional monoclonal antibodies due to their unique structural and functional capabilities. As a next generation of nanobiotechnology, natural and synthetic nanobodies have been utilized in numerous fields of biomedicine, including as biomolecular materials, for various biological studies, and in medical diagnostics and immunotherapy (Tang et al. 2023).

Monoclonal antibodies and their use in the treatment of infectious diseases

The development of monoclonal antibody use for the treatment of infectious diseases is relatively recent compared to their applications in oncology and the management of autoimmune diseases. Their medical indications remain limited to the prevention of bronchiolitis caused by respiratory syncytial virus (RSV), treatment of drug-resistant HIV infection, exposure to the rabies virus, pulmonary anthrax, prevention of recurrent diarrhea caused by Clostridium difficile, and atypical hemolytic uremic syndrome caused by Escherichia coli. In the near future, emerging technologies are expected to accelerate the development of anti-infective monoclonal antibodies, significantly expanding the therapeutic arsenal for antibacterial and antiviral treatments (Desoubeaux and Pelegrin 2019).

Respiratory tract infections are the third leading cause of morbidity and mortality worldwide in both children and adults, accounting for approximately 4.25 million deaths annually (Schluger and Koppaka 2014). Beyond premature mortality, respiratory infections have a profound impact on society and the economy due to the disability they cause and the associated healthcare costs for treatment and care (Mayor et al. 2021). Respiratory tract infections encompass a wide range of diseases affecting both the upper respiratory tract (rhinitis, sinusitis, pharyngitis, tracheitis) and the lower respiratory tract (primarily bronchitis and pneumonia). These infections have diverse etiological agents, including viruses, bacteria, and fungi (Liu et al. 2016).

Viral respiratory infections represent a major global health concern due to their status as the most common cause of illness, leading to significant economic losses from a high number of sick leave days (DeVincenzo et al. 2020). Among the primary causative agents of respiratory viral infections are influenza viruses (A and B) and respiratory syncytial virus (RSV) (Heylen et al. 2017; Yip et al. 2018). Some of these viruses have been present in human populations for centuries, while others, such as SARS-CoV-1, MERS, and SARS-CoV-2, have emerged as new threats to humanity. For example, humans have long been exposed to influenza viruses; however, their ability to rapidly evolve through antigenic drift and antigenic shift results in the continuous emergence of new strains. A recent example of this phenomenon is the avian-origin H7N9 influenza virus, which caused an outbreak in China. This virus is resistant to amantadine treatment, and some strains have also shown resistance to neuraminidase inhibitors, significantly limiting therapeutic options for managing the infection (McKimm-Breschkin et al. 2018). Respiratory syncytial virus (RSV) can cause lower respiratory tract

infections, such as bronchiolitis and pneumonia, primarily in children and the elderly. RSV infections lead to severe illnesses and even fatalities, presenting significant challenges for pediatrics and geriatrics worldwide. The severity of these diseases often stems from the lack of effective or, in some cases, any etiological treatment. In most cases, management is supportive, with the only approved therapy for RSV being a monoclonal antibody used prophylactically in high-risk patients (Boivin et al. 2008). Palivizumab is the first antiviral monoclonal antibody approved by the U.S. Food and Drug Administration (FDA) for prophylaxis against RSV in high-risk neonates (Boivin et al. 2008). The Middle East respiratory syndrome coronavirus (MERS-CoV) serves as an example of an emerging respiratory virus. First isolated in 2012, MERS-CoV causes severe lower respiratory tract infections, predominantly in patients with comorbidities. Currently, there are no licensed vaccines or drugs approved for the treatment of MERS-CoV-related disease. Nevertheless, a wide range of medications has been employed to combat the virus, with their use primarily informed by knowledge gained during the SARS-CoV-1 outbreaks in 2003 and the influenza pandemic in 2009 (Mo and Fisher 2016). These examples underscore the critical need for the development of new antiviral drugs that can be used alone or in combination with existing treatments to combat these serious, humanity-threatening respiratory viral infections (Behzadi and Leyva-Grado 2019).

Monoclonal antibodies and antibody-based molecules—reliable opportunity to effectively counter emerging viral pathogens and antibiotic-resistant bacteria

After more than 60 years marked by the widespread use (bordering on abuse) of broad-spectrum antibiotics, "constitutional" resistance to antiviral medications and antibiotic resistance in most microorganisms responsible for secondary bacterial and fungal infections (superinfections) have become a real threat. Against this backdrop, the need for drugs with a new mode of action to complement the existing conventional therapeutic arsenal is real. Monoclonal antibodies and antibody-based molecules offer a reliable opportunity to effectively counter emerging viral pathogens and antibiotic-resistant bacteria (Jin et al. 2017; Salazar et al. 2017; Domenech et al. 2018). The pioneering work of Emil von Behring and his development of the diphtheria antitoxin serum actually laid the foundations for the long

journey toward the modern use of antibodies in infectious diseases (Desoubeaux et al. 2016; Mayor et al. 2021).

Antibodies have several advantages over other antimicrobial medications. First, they provide a treatment option when available drugs fail, there are no corresponding vaccines, or existing conventional treatments are ineffective due to a compromised immune system or because the microorganism has developed resistance. Second, antibodies are specifically targeted toward highly conserved and precisely defined antigens, which minimizes the possibility of drug resistance developing. Last but not least, when administered to patients with a healthy immune system, they can provide necessary prophylaxis against specific diseases, acting as vaccine-like molecules, promoting long-term, antimicrobial-specific immune responses (Pelegrin et al. 2015).

The development of monoclonal antibodies in the field of infectious diseases is as necessary as it is complex. A number of scientific, regulatory, and even commercial barriers need to be overcome before this class of drugs becomes widely accessible to patients (Mayor et al. 2021). Of the monoclonal antibodies approved by the U.S. Food and Drug Administration (FDA), only 8% are for the treatment of infectious diseases. The high production cost, low stability, and large size of the molecules, which contribute to some of their "drawbacks," are likely the main obstacles to the rapid and widespread adoption of monoclonal antibodies for the treatment of various infections.

Nanoantibodies and infectious diseases

As already described, nanoantibodies are increasingly finding their place in the field of infectious diseases due to their lower production cost, higher stability, lower immunogenicity, potential for inhalation application, and their small "size." Their special structure and advantages are the reasons for their increasing use in the field of structural biology (Warne et al. 2019; Uchański et al. 2020), for the discovery of various biochemical mechanisms (Drees et al. 2016), molecular visualization (Traenkle and Rothbauer 2017), and the diagnosis and treatment of tumors (Feng et al. 2021) and infectious diseases (Weiss and Verrips 2019; Tremblay et al. 2020). Nanoantibodies in the field of infectious diseases are primarily used in the diagnosis and treatment of viral infections. In the last two decades, the pathogens of epidemics have been RNA viruses—SARS-CoV-1 in 2003, H1N1 influenza virus in 2009, MERS-CoV virus in 2012, and SARS-CoV-2 virus in 2019 (Huang et al. 2022). This is no coincidence, as it is due to the main characteristics of RNA viruses, namely high transmissibility and high mutation potential (Huang et al. 2022). This specificity leads to a lack of sufficiently effective drugs and vaccines for the treatment and prevention of severe infections. Most of the nanoantibodies being developed could be used as therapeutic agents against respiratory RNA viral infections by inhibiting the virus's entry into cells or inhibiting viral replication and the release of virion progeny (Marasco and Sui 2007). In addition to the mentioned advantages of nanoantibodies, they have the ability to penetrate "deep" into the sterically hidden interface of viral particles, thereby neutralizing them. These small antibodies can easily be designed as multivalent and thus possess greater neutralizing potential (Wu et al. 2017). Possible inhalational application ensures direct action on the "lining" of the airways as the primary entry point for most viral and bacterial infections. On the other hand, the bronchopulmonary system is the most common target of viral and bacterial pathogens (Li et al. 2022). This specific subgroup of drugs has the potential to provide universal antiviral treatment for RNA respiratory viral infections, as well as contribute to the design of effective vaccines. The group also holds potential in combating rare inhaled toxins carrying antigenic markers. Despite all the described advantages, the use of conventional monoclonal antibodies still outpaces that of nanoantibodies in the treatment of respiratory viral infections. A likely limitation to their widespread use is their short half-life in vivo. Significant efforts are being directed towards extending their plasma half-life, such as by binding antiviral nanoantibodies to anti-human serum albumin in the form of an "anti-human serum albumin-nanoantibody" complex or to IgG1-type Fc fragments (Huang et al. 2022). It is important to note that a large number of nano-mAbs are being developed specifically for targeting the SARS-CoV-2 virus (Wu et al. 2017; Qin et al. 2022).

Nanomonoclonal antibodies (Nano-MAB), as previously mentioned, offer significant advantages over conventional monoclonal antibodies, including the potential for inhalation-based application, direct administration to infected tissues, rapid absorption, high local concentration with high bioavailability, and, not least, excellent patient compliance (eliminating the need for injectable administration). We have outlined their great potential in the treatment of respiratory viral infections. The rapid and relatively inexpensive development of nanobodies against the SARS-CoV-2 virus and its mutant strains helps limit the virus's ability to "escape" the neutralizing effects of antibodies and the emergence of new virus variants (VOCs). Nano-MABs hold full potential to complement the pharmacological arsenal against COVID-19 (Chen et al. 2021).

The first nanobody (Caplacizumab) was approved by the EMA/FDA in 2018/2019 for the treatment of acquired thrombotic thrombocytopenic purpura (aTTP) in adult patients. Numerous studies have focused on the use of these nanobodies for various viral diseases, including dengue virus, hepatitis B virus, hepatitis C virus, poliovirus, norovirus, and Ebola virus. These studies are promising regarding the prospects of using nanobodies against the SARS-CoV-2 virus (Chen et al. 2021).

Another advantage of this unique class of antibodies is their stability—even during long-term storage, their biological activity is not compromised. This implies their potential for preservation as a reserve for emergency use and specific treatment, such as during the peak waves of the coronavirus pandemic. Multivalent nanobodies are also highly promising in preventing the emergence of new viral mutations. The combination of two nanobodies with

complementary mechanisms of action can inhibit the interaction between ACE2 and RBD, effectively neutralizing the original SARS-CoV-2 virus and N501Y-D614G variants at relatively low concentrations (Pymm et al. 2021).

COVID-19 infection and monoclonal antibodies—a potentially effective therapy

The coronavirus pandemic has profoundly transformed healthcare systems worldwide since the first confirmed cases of SARS-CoV-2 infection emerged in 2019. COVID-19 spread globally at an unprecedented pace, with identified clinical cases surfacing as early as the first months of 2020. The pandemic had a devastating impact on public health and the global economy (Wood et al. 2023). Although the imposed isolation and preventive measures had a temporary effect (albeit poorly timed and incompetently implemented in terms of scope and duration) on limiting the spread of the infection, subsequent outbreaks occurred both during and after the lifting of social restrictions (Chen et al. 2021). With the initiation of COVID-19 vaccination campaigns, authorities removed many of the measures designed to curb disease transmission, only to face a new challenge: the rapid emergence and spread of new SARS-CoV-2 variants, leading to an increase in cases during the spring and summer of 2021 (Wood et al. 2023). Since the World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020, more than 6 million deaths have been reported worldwide—a mortality rate that, while significant from a philosophical standpoint, we believe does not equate to the scale of the health crisis during the 1918 influenza pandemic, as suggested by some authors (COVID-19 Excess Mortality Collaborators 2022; Aleem et al. 2023). The majority of SARS-CoV-2-infected patients experience mild or asymptomatic disease, presenting with banal respiratory symptoms commonly associated with influenza and other respiratory viral infections, such as fever, mild shortness of breath, cough, and general fatigue. However, in a subset of patients (currently lacking a representative statistical sample for moderate and severe cases on a global population scale), severe pneumonia develops, often accompanied by respiratory failure, necessitating supplemental oxygen therapy, intensive care, and, in some cases, progression to acute respiratory distress syndrome (ARDS). This severe form of the disease largely determines the mortality associated with COVID-19 infection (Fan et al. 2020).

The clinical forms of COVID-19 can be classified based on the clinical presentation as follows:

- Asymptomatic or presymptomatic infection: A positive SARS-CoV-2 test without clinical manifestations of COVID-19 infection.
- Mild infection: Patients with clinically evident COVID-19 infection but without dyspnea, shortness of breath, or radiological findings in the lungs.
- Moderate infection: Clinical and radiological evidence of pneumonia without hypoxia (Sat. atm ≥ 94%).
- Severe infection: Hypoxia (SpO2 < 94%), a ratio of arterial partial oxygen pressure to inspired oxygen fraction (PaO2/FiO2) < 300 mmHg, respiratory rate > 30 breaths per minute, or lung infiltrates involving more than 50% of the lung volume.
- Critical infection: Patients with severe respiratory failure, septic shock, and/or multiorgan dysfunction (Elsaghir and Adnan 2023).

Mild and moderate forms of the disease are typically managed in pre-hospital medical care. Patients requiring oxygen therapy are hospitalized, often necessitating intensive care, noninvasive or invasive ventilation, and treatment for secondary infections. The management of non-hospitalized patients requires proper triage to assess symptom severity and identify potential for clinical progression or deterioration. The development of acute respiratory distress syndrome (ARDS) is attributed to impaired innate immunity, inadequate adaptive immune responses, uncontrolled virus-induced and inflammation-induced tissue damage, and increased vascular permeability, creating a "terrain" for severe disease progression (Polidoro et al. 2020). The pathogenesis of COVID-19 unfolds in two phases:

1. Early phase: Characterized by rapid replication of the SARS-CoV-2 virus.
2. Late phase: Characterized by inflammation mediated by cytokine release, including tumor necrosis factor-alpha (TNF-alfa), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-1 (IL-1), IL-6, interferon-gamma (IFN), and activation of the coagulation system in a prothrombotic state.

Ultimately, the disease outcome in the late phase is either recovery or complications leading to treatment-resistant septic conditions with multiorgan failure and fatal outcomes. Antiviral medications and antibody-based therapies are most effective during the early phase of the disease. On the other hand, immunomodulatory therapy, used alone or in combination with antiviral drugs and monoclonal antibodies, is more effective when applied during the late phase. This approach targets the cytokine-mediated hyperinflammatory state, which underlies the severe forms of the disease (Wood et al. 2023).

During the coronavirus crisis, extraordinary biomedical and financial resources were allocated to rapidly develop diagnostic, preventive, and therapeutic solutions to combat the emerging threat posed by the SARS-CoV-2 virus and the disease it causes, COVID-19. Due to their high specificity and multifunctionality, monoclonal antibodies have taken a prominent position in the therapeutic arsenal against COVID-19. Monoclonal antibodies are increasingly being utilized in the treatment of viral infections because of their ability to prevent disease progression immediately after administration and to enhance recovery processes, regardless

of whether the patient has developed a full immune response to the infection (Hwang et al. 2022).

Several strategies exist for the development of new therapeutic agents against coronavirus infections. These include the empirical testing of already known and used antiviral drugs, large-scale phenotypic screening of various compounds, and the discovery of new targeted therapies (primum non nocere!). To date, an increasing number of compounds have demonstrated in vitro anti-coronavirus activity (Mei and Tan 2021), although in our view, the anticipated in vivo effect is not always observed. Nevertheless, their therapeutic potential and clinical application remain limited and are specific to certain stages of the disease (Aleem and Vaqar 2023). Monoclonal antibodies have been identified as a potentially effective therapy for preventing the progression of COVID-19 in patients at high risk of developing severe disease (Elsaghir and Adnan 2023). Advances in antibody engineering technologies, deeper understanding of viral biochemistry, and insights into the direct and indirect effects of synthesized antibodies on the course of viral infections have resulted in the development of numerous new monoclonal antibodies. Like other antiviral medications, monoclonal antibodies are not immune to the development of "resistance," which results from alterations in the viral genome. These changes modify the virus's pathogenic potential, ultimately leading to the emergence of mutant viruses—so-called "escape variants." These variants spread rapidly and become resistant to the neutralizing effects of the respective monoclonal antibodies. To counteract this phenomenon, known as "viral escape," combinations of monoclonal antibodies—referred to as "antibody cocktails"—are used. These cocktails combine two specific monoclonal antibodies with complementary mechanisms of action, targeting multiple viral epitopes. This strategy significantly reduces the likelihood of the virus escaping the neutralizing activity of the treatment. Various monoclonal antibodies, differing in function, are continuously being developed or are already in clinical trials for the treatment of COVID-19 (Aleem et al. 2023).

Initially, treatment efforts were focused mainly on hospitalized patients. However, as the COVID-19 pandemic expanded, it became evident that shifting the clinical focus to the early phases of infection was critical to reduce viral load and prevent disease progression. This is where monoclonal antibodies play a pivotal role. They are particularly effective in treating non-hospitalized patients with mild to moderate infections who are at high risk of developing severe COVID-19 (Wood et al. 2023).

The SARS-CoV-2 virus and the immune response to it

The SARS-CoV-2 virus is the third highly pathogenic human coronavirus, belonging to the Betacoronavirus genus and containing positive-sense single-stranded RNA (Maghsood et al. 2022). It comprises four major structural proteins: the spike glycoprotein (S), forming the characteristic spikes on the viral envelope; the membrane glycoprotein (M); the envelope protein (E), which is transmembrane; and the hemagglutinin-esterase dimer protein (HE), which exhibits acetyl-esterase activity. Its genome is an RNA sequence approximately 30,000 bases (30 kb) in length. The virus enters host cells by binding the SARS-CoV-2 spike S1 protein to the membrane-bound angiotensin-converting enzyme II (ACE2) protein. ACE2 is expressed on respiratory cells (type II alveolar cells, upper airway epithelial cells) as well as other cells in the body, such as endothelial cells, kidney cells, and ileal epithelial cells (Mayor et al. 2021). This process is mediated by the receptor-binding domain (RBD) of the spike protein, followed by the priming of the spike protein's S2 domain by the host cell's transmembrane serine protease 2 (TMPRSS2), facilitating viral entry and replication. Monoclonal antibodies prevent viral attachment by binding with high affinity to non-overlapping epitopes on the RBD of the SARS-CoV-2 spike protein. This action blocks the virus from binding to the ACE2 receptor (Aleem et al. 2023).

A significant part of the knowledge accumulated so far regarding the immune response to SARS-CoV-2 comes from the extensive body of studies published since the beginning of the pandemic, as well as from comparisons with past experiences from the SARS-CoV-1 and MERS-CoV epidemics. Many mechanisms underlying the development and progression of coronavirus infection in patients have been thoroughly studied; however, the pathogenesis of COVID-19 remains to be fully elucidated. Briefly, after the S glycoprotein binds to the ACE2 receptor and the SARS-CoV-2 virus enters the cell, fusion of the viral capsid (viral envelope) with the cell membrane occurs. This process is mediated by the serine protease TMPRSS2 (transmembrane serine protease) and the endosomal cysteine proteases cathepsins B and L. Once the SARS-CoV-2 viral RNA is released into the cell, its replication begins. Following the formation of mRNA, transcription and subsequent translation processes commence using the cellular organelles, leading to viral replication. Once the newly formed viruses are assembled, they are released extracellularly via budding and exocytosis. This process concludes with cellular death, leading to functional and structural destruction of the host cell. SARS-CoV-2 is a pathogenic cytotropic virus that causes direct cellular death during viral replication, resulting in tissue damage and an increased inflammatory response (Mayor et al. 2021).

The immune response against the viral infection starts at the cellular level and plays a critical role in the pathogenesis of COVID-19 (Sariol and Perlman 2020). On the one hand, SARS-CoV-2 induces antiviral immune responses by activating both the innate and adaptive immune systems in an attempt to control the viral infection. These processes begin in the endosomal compartment of infected cells through signaling pathways triggered by pattern recognition receptors, such as Toll-like receptor 3. These pathways ultimately lead to the production of inflammatory cytokines, which, in turn, activate im-

mune-competent cellular populations. Cells of the innate immune system are activated by the released cytokines and damage-associated molecular patterns (DAMPs). Under certain conditions, they are capable of inducing an adaptive immune response. In fact, these are cells of the leukocyte population (commonly referred to as leukocytes). Often in the modern scientific landscape, some authors incorrectly refer to certain immunocyte subpopulations as "dendritic" cells. However, it is appropriate for every cellular population/subpopulation to be named according to its embryonic origin and histological classification. These leukocytes, primarily macrophages (including phagocytic granulocytes) and activated immunocytes—cells mediating antigen presentation (B lymphocytes)—constitute the backbone of adaptive immunity.

On the other hand, SARS-CoV-2 can also elicit a pathological immune response. Viral invasion of the target cell leads to suppression of the ACE2 receptor, causing an imbalance in the renin-angiotensin system and resulting in angiotensin II-induced increased vascular permeability and the development of pneumonia with associated vascular damage (Blanco-Melo et al. 2020; Mayor et al. 2021). Furthermore, activation of type 1 angiotensin II receptors directly stimulates NF-kB and ADAM17, ultimately resulting in uncontrolled production of tumor necrosis factor-alpha (TNF-alfa) and interleukin-6 (IL-6) (Blanco-Melo et al. 2020). In the pathogenesis of pulmonary inflammation caused by the SARS-CoV-2 virus (COVID-19 pneumonia), activated alveolar macrophages and pulmonary epithelial cells are the main producers of these mediators. This, in turn, mediates a systemic myelopoietic reaction and locally increases the expression of cellular adhesion molecules and vascular endothelial growth factor (VEGF) (Polidoro et al. 2020). The increased pulmonary vascular permeability resulting from these processes facilitates viral dissemination as well as leukocyte infiltration, underpinning local inflammation. Together with systemic inflammatory effects, this leads to the development of acute respiratory distress syndrome (ARDS) (Mayor et al. 2021).

Monoclonal antibodies with a direct antiviral effect and monoclonal antibodies (mAbs) with a specific anti-inflammatory effect

A significant number of antibodies have been developed to address the SARS-CoV-2 pandemic (Chen et al. 2021; Mayer et al. 2021; Mei and Tan 2021; Li et al. 2022; Maghsood et al. 2022; Aleem et al. 2023). These can be categorized into two main groups. The first category of anti-SARS-CoV-2 antibodies is aimed at symptom reduction and consists primarily of well-known antibodies with mechanisms of action targeting the intense inflammatory response. These are monoclonal antibodies (mAbs) with a specific anti-inflammatory effect. They exert immunosuppressive effects on particular immunocompetent cells as well as other cellular populations involved in the inflammatory process. This group reduces specific cellular populations through antiproliferative and/or direct cytotoxic effects. Some of these antibodies also exert direct suppressive or blocking effects on specific cytokines or target epitopes within the complement cascade. Therapeutic antibodies that inhibit cytokine activity can mitigate the harmful effects of a hyper-stimulated immune system in some patients and, through this mechanism, may be used in the treatment of COVID-19 (Hwang et al. 2022). In cases of severe inflammatory processes of infectious origin, such modulation of the immune response is justified but always carries a risk of further destabilizing the dynamic equilibrium between stimulatory and inhibitory immune mechanisms in the specific organism. The second category includes monoclonal antibodies with a direct antiviral effect. These are pharmaceutical agents used in mAb-based therapies specifically targeting the SARS-CoV-2 virus (Mayor et al. 2021).

SARS-CoV-2 variants of concern—emerging theories and the role of monoclonal antibodies

The replication mechanism of coronaviruses encodes proofreading functions, resulting in fewer errors compared to other RNA viruses. Nevertheless, numerous SARS-CoV-2 variants of concern (VOCs) have continued to emerge since the start of the pandemic, carrying so-called VOC-defining mutations. For example, Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta, Zeta, Eta, Theta, Iota, and Omicron variants contain specific sets of mutations that enable them to evade the natural neutralizing activity of antibodies as part of the immune response in infected individuals (Ai et al. 2022; Huang et al. 2022; Gupta et al. 2023). The evolution of the SARS-CoV-2 virus from its identification in 2019 to the present has led to the emergence of variants with increased transmissibility and virulence (Jang et al. 2023).

The Delta variant was first identified in India in November 2020 and exhibits approximately 60% greater transmissibility compared to the Alpha variant (Mahase 2021). Due to this, the Delta variant rapidly became the dominant circulating strain in many countries worldwide. In addition to its faster spread, the Delta variant is associated with significantly higher rates of hospitalization among infected individuals (Taylor et al. 2021). These characteristics have inevitably exacerbated the epidemiological situation, straining healthcare systems regardless of vaccine availability. Furthermore, the efficacy of RNA-based vaccines during the pandemic period requires impartial investigation and precise evaluation. By the end of 2021, global COVID-19 vaccination programs had administered 8.6 billion vaccine doses, leaving approximately 40% of the global population unvaccinated.

It is understood within the scientific community that the aforementioned data cannot claim to be comprehensive. There remain human populations on our planet that are inaccessible for any representative studies. Nevertheless, these populations are not excluded from the biological analysis of the pandemic situation. Numerous studies on vaccine efficacy against Delta variant infections have demonstrated that vaccination is 10–20% less effective in preventing symptomatic infection with the Delta variant compared to the Alpha variant. However, vaccine efficacy in preventing hospitalization remains equivalent for both variants (Jang et al. 2023). Data from post-vaccination COVID-19 outbreaks in India indicate that more than 50% of confirmed infections were caused by the Delta variant (Gupta et al. 2021).

Given that a "non-determinable" portion of the global population remains unvaccinated, coupled with the continuous emergence of new viral variants and the proven potential for breakthrough infections in vaccinated individuals, the need for effective drug therapy against COVID-19 remains critical (Jang et al. 2023). In addition to the existing therapeutic arsenal, monoclonal antibodies (mAbs) that directly target SARS-CoV-2 and disrupt its viral replication cycle have been assigned a particularly significant role (Baral et al. 2021; Corti et al. 2021). These novel agents have demonstrated their greatest utility and efficacy during the Delta variant's period of dominance, during which they were most widely used and thoroughly studied.

The Omicron variant, harboring more than 30 mutations in the viral spike protein and 15 mutations in the receptor-binding domain (RBD)—the primary target for virus-neutralizing antibodies—stands out significantly compared to other variants, which typically have no more than three RBD mutations. Omicron has demonstrated remarkable resistance to the neutralizing activity of serum antibodies, thereby compromising the protective efficacy of vaccines and likely therapeutic monoclonal antibodies (Cameroni et al. 2022; Cao et al. 2022; Cele et al. 2022). Notably, the majority of RBD mutations in the Omicron variant (9 out of 15) affect the ACE2 receptor-binding motif (RBM), while the remaining six are located on the protruding core of the RBD. However, key regions, including the buried section within the spike protein trimer and the cryptic lateral surface, remain largely unchanged. Identifying highly conserved epitopes across SARS-CoV-2 variants is critical for the development of broadly neutralizing antibodies and, potentially, universal vaccines (Li et al. 2022).

Casirivimab and Imdevimab (CAS+IMD) are a combination of two monoclonal antibodies that bind to non-overlapping epitopes within the RBD of the SARS-CoV-2 spike protein (Baum et al. 2020). This combination, initially used for strains sensitive to its activity, received approval in the United States for COVID-19 treatment and post-exposure prophylaxis under specific conditions. Preclinical data indicate reduced neutralizing activity of CAS+IMD against the Omicron variant but robust activity against other variants (Somersan-Karakaya et al. 2022). Studies conducted before Omicron's widespread circulation demonstrated that the administration of CAS+IMD reduced hospitalization, mortality, viral load, and illness duration in COVID-19 patients (O'Brien et al. 2021; Weinreich et al. 2021). Published data also indicate high efficacy of CAS+IMD in preventing infection and symptomatic disease when administered shortly after SARS-CoV-2 exposure to asymptomatic individuals (O'Brien et al. 2021). The greatest therapeutic benefit of CAS+IMD is observed when treatment is initiated early in the course of infection (Verderese et al. 2022). Based on the potential antiviral activity of Casirivimab and Imdevimab, it is hypothesized that reducing viral load in the early stages of infection could significantly lower morbidity and mortality associated with COVID-19 in hospitalized patients.

Adding this "cocktail" of antibodies to the standard treatment significantly reduces the overall mortality rate in treated patients, marking the first mAb therapy against the SARS-CoV-2 virus where these effects have been proven (Somersan-Karakaya et al. 2022). The mechanism of action of CAS+IMD, as well as its safety profile, allows it to be combined with other medications, such as some interleukin-6 inhibitors (IL-6) like tocilizumab and sarilumab, which are recommended by the World Health Organization (WHO) for use in hospitalized patients and have been shown to reduce mortality by 13% in these patients. The combination with Janus kinase inhibitors like Baricitinib is also promising, given its potential to improve 28-day survival by 38% in hospitalized patients (Marconi et al. 2021). Overall, casirivimab and imdevimab reduce viral load and therefore improve the clinical course of the disease when administered timely, with significant benefit in seronegative patients and no observed harm to seropositive individuals. CAS+IMD maintains good neutralizing activity against all "variants of concern" (VOCs), including the Delta variant (Copin et al. 2021), but shows significantly reduced activity against the Omicron variant. The clinical outcomes of this combination are promising with regard to the potential for neutralizing activity in treated patients and the future development of mAb therapy against COVID-19 (Somersan-Karakaya et al. 2022). The Casirivimab and Imdevimab combination is a medication used for the treatment of COVID-19 in adults and adolescents (over 12 years of age and weighing at least 40 kg) who do not require additional oxygen and are at high risk for developing severe disease. The drug can also be used for COVID-19 prevention in people aged 12 and older who weigh at least 40 kg. On 21 November 2020, the drug was granted Emergency Use Authorization (EUA) by the U.S. Food and Drug Administration (FDA), and a year later, it received the same indication from the European Medicines Agency (EMA) (Kaplon et al. 2022).

Regdanvimab is a neutralizing antibody that prevents the interaction of the SARS-CoV-2 virus with the angiotensin-converting enzyme 2 (ACE2) receptor, thus hindering its entry into epithelial and endothelial cells (Jang et al. 2023). In studies conducted with patients with moderate COVID-19, those treated with regdanvimab showed reduced viral load and shorter recovery time compared to

the placebo control group (Kim et al. 2021). A significant reduction in the number of patients requiring hospitalization and oxygen therapy and a decrease in mortality were observed in patients with mild to moderate COVID-19 infection treated with regdanvimab (Jang et al. 2023).

The fight against the "cytokine storm"

In addition to direct antiviral immune therapy in the context of already complicated COVID-19 infection, clinicians face an extremely serious challenge—the fight against the so-called "cytokine storm."

Cytokine storm represents a syndrome of uncontrolled systemic inflammatory response associated with extremely elevated levels of inflammatory cytokines in response to various stimuli, including medications, pathogens, or autoimmune diseases. For critically ill COVID-

19 patients, this syndrome is characterized by malignant fever, severe pneumonia, development of respiratory distress syndrome, and multi-organ failure, with a high mortality rate in these cases. The development of cytokine storm is responsible for the severe forms of COVID-19. Although the role of inflammatory factors in the treatment of SARS-CoV-2 viral infection is not fully clarified, effective neutralization of the overproduced inflammatory factors in cytokine storm syndrome is crucial for reducing mortality in COVID-19 patients (Hwang et al. 2022). In addition to interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor (TNF), several other factors associated with cytokine storm are potential therapeutic targets for the treatment of severe COVID-19 infection. Persistently elevated levels of IL-6 in patients with a hyperinflammatory response suggest that this cytokine is a key mediator of the cytokine storm, although the exact mechanisms of its action are not fully understood (Sinha et al. 2020). For example, several monoclonal antibodies targeting IL-6 can be used to treat severe COVID-19 infection, including Sarilumab, Tocilizumab, Levilimab, Clazakizumab, Siltuximab, and Olocizumab (Hwang et al. 2022). TNF is a key cytokine in the pathogenesis of many inflammatory diseases, as it regulates IL-6 expression. Unlike anti-IL-6 therapy, anti-TNF monoclonal antibodies reduce the secretion of several cytokines such as IL-1, IL-6, and GM-CSF (granulocyte-macrophage colony-stimulating factor). There are three important cytokines from the IL-1 family that are highly responsible for cytokine storm: IL-1β, IL-8, and IL-33. Among them, blocking IL-1β holds great potential for counteracting cytokine storm. Canakinumab is a human antibody that neutralizes the bioactivity of IL-1β by competing for binding with IL-1RI and is approved for the treatment of cryopyrin-associated periodic syndrome (CAPS) and other serious autoimmune

diseases. Clinical trials are ongoing to establish the efficacy and safety of canakinumab in patients with COVID-19 (Landi et al. 2020; Ucciferri et al. 2020). GM-CSF is also elevated in COVID-19 patients, and its binding to the GM-CSF receptor-α (GM-CSFR-α) stimulates the production of IL-1, IL-6, and TNF, enhancing Janus kinase 2 (JAK2) signaling. Mavrilimumab is a human monoclonal antibody targeting GM-CSFR-α, currently undergoing clinical trials for the treatment of rheumatoid arthritis. Promising data have emerged for therapeutic monoclonal antibodies against GM-CSF and their ability to improve the clinical course of infection in the treatment of COVID-19 (Hwang et al. 2022). Monoclonal antibodies targeting IL-6, IL-1, IL-17, IL-23, and TNF-α receptors could reduce mortality in COVID-19 patients and are a promising addition to the existing treatment for SARS-CoV-2 infection, considering the lack of serious side effects and good tolerance (Kirillova et al. 2022). Of course, the modulation of inflammation in all infectious diseases should be performed with strict indications and control. It should not be forgotten that the effect of monoclonal antibodies used for this modulation is necessarily reflected in the immune response. When analyzing the clinical picture of each patient, it is appropriate to base the philosophy on the idea that every inflammatory process is, to some extent, also a protective response of the body.

SARS-CoV-2, vaccines, monoclonal antibodies, and the appearance of new mutations

The continuous emergence of new variants of the SARS-CoV-2 virus underscores the urgent need for the development of broad-spectrum vaccines and new monoclonal antibodies. Mutations in the Omicron variant are responsible for the reduced protective effect of vaccines against it. Moreover, these mutations allow the "modified" virus to "evade" antibody binding, particularly when the antibodies target epitopes overlapping with the ACE-2 binding sites. Human nanoantibodies, for example, not only have a good safety profile and clinical efficacy but also enhanced activity against the Omicron variant. The bispecific nanoantibody bn03 has the capacity to bind to two different epitopes on the RBD of the SARS-CoV-2 Omicron variant, both simultaneously and synergistically. Due to its unique profile, such an antibody could have a broad spectrum of activity against both existing viral variants and newly emerging ones (Li et al. 2022). As it has been established, no vaccine provides 100% efficacy in preventing symptomatic forms of COVID-19. After vaccination, some individuals do not generate any immune response, or they generate only a weak and insufficient immune response (Sharma et al. 2020), while others may develop an infection (including complicated cases) after encountering the virus, despite being vaccinated (Hacisuleyman et al. 2021; Lange et al. 2021). Additionally, the unequal distribution of vaccines worldwide, their time-limited immunization effect, and the rapid emergence of new viral variants with the capacity to reduce vaccine efficacy demonstrate that vaccines alone are insufficient to control the pandemic (Callaway 2021; Hwang et al. 2022). This highlights the

need not only for the development of new medications but also for a comprehensive understanding of the immunity established in patients after recovery, how it is affected by treatment, and its subsequent monitoring and evaluation. It has been found that the rate of SARS-CoV-2 mutations is higher in immunocompromised or critically ill patients who experience prolonged COVID-19 infection or have prolonged (including "silent" - "silent carrier") viral shedding (Andreano et al. 2021; Valesano et al. 2021; Lee et al. 2022). Immunocompromised patients exhibit an inability to generate an effective neutralizing antibody titer after receiving COVID-19 vaccines. Due to these facts, several synthetic neutralizing antibodies, some of which we have already mentioned, were developed against the coronavirus and primarily targeted the viral spike (S) protein. These have shown very good clinical results (Gupta et al. 2021; Planas et al. 2022; Savoldi et al. 2022). Patients treated with monoclonal antibodies develop undetectable spike mutations at a remarkable rate and with high specificity to the

target monoclonal antibody-binding region. Immunocompromised patients treated with monoclonal antibodies have proven prolonged and significant viral shedding, as well as a tendency to develop "de novo" spike protein mutations. The development of mutations strongly correlates with the neutralizing capacity of the therapeutic monoclonal antibody and T-cell immunity, suggesting the important role of a strong immune response in the emergence of viral mutations. These findings are critical when making decisions about patient treatment, minimizing the risks of unsuccessful therapy with monoclonal antibodies, and improving strategies to combat the spread of viral mutants (Gupta et al. 2023).

Immunocompromised patients infected with the Omicron variant of the SARS-CoV-2 virus exhibit higher viral loads following monoclonal antibody treatment. Therapeutic titers of monoclonal antibodies are not directly associated with the development of S RBD mutations. Their neutralizing capacity is merely a trigger for the emergence of new viral variants, with a significant role played by the "naturally" acquired T-cell immunity. Existing immunity against the SARS-CoV-2 virus, whether due to current or past exposure, vaccination, or variations in the immune system of the infected individuals, can significantly influence the outcome of the disease in patients treated with various monoclonal antibodies. There is a hypothesis suggesting that the less hospitable the immune system of the infected patient is to the virus and the more intense the tissue repair due to the infection, the more this contributes to enhancing the cycles of viral replication in infected cells. This, in turn, leads to rapid viral evolution, driven by immune pressure, "catalyzed" by the application of monoclonal antibodies.

Several authors argue that de novo S RBD mutations are unequivocally "monoclonal antibody-specific," and furthermore, they accumulate more quickly during the acute phase of infection, peaking within 7 days of starting treatment (Gupta et al. 2023). Some studies suggest that the immune status associated with chronic COVID-19 infection or severe forms of the disease predisposes to the emergence of SARS-CoV-2 viral mutations (Braun et al. 2021; Tonkin-Hill et al. 2021; Valesano et al. 2021). However, recent data contradict the earlier claims that the severity of infection and its chronic course are factors contributing to the emergence of new mutations. With an adequately effective and rapid immune response, such as the one achieved in an intact immune system and with appropriate monoclonal antibody treatment, timely eradication of the virus leaves no room for mutagenic reproductivity. Both RNA and DNA viruses have the ability to generate de novo mutations relatively quickly during the adaptation process to a new host, i.e., to a new environment. The common factor in all studies investigating the causes of mutations in the SARS-CoV-2 virus, leading to the circulation of new viral variants with epidemic potential, is that viral mutation processes occur primarily in immunocompromised patients. Additionally, the higher the viral load in an infected patient, the higher the likelihood of S RBD mutations.

Two specific components of the immune response to COVID-19 infection have been identified, which are associated with a greater likelihood of new viral variants emerging. The first is the suppression of pro-inflammatory cytokines, which leads to reduced viral clearance, more viral replication cycles, and increased opportunities for viral adaptive changes, manifested as mutations. Secondly, in patients developing de novo viral mutations, a stronger T-cell immune response has been observed following monoclonal antibody therapy, demonstrating the role of strong immune pressure on the virus in triggering its adaptive mechanisms (Andreano and Rappuoli 2021). It is believed that almost all viral variations of the SARS-CoV-2 virus arise in immunocompromised patients, who are characterized by prolonged viral shedding. These findings highlight the need to optimize strategies for treating

immunocompromised patients with monoclonal antibodies in order to reduce the risk of spreading new SARS-CoV-2 variants to other high-risk patient groups, both in hospital and outpatient settings. The facts presented thus far demonstrate the importance of both the neutralizing capacity of therapeutic monoclonal antibodies and the strength and adequacy of the immune response in infected patients against the SARS-CoV-2 virus for the development of new viral variants. The balance between definitive viral eradication and the emergence of new variants of concern (VOC) is critical. The development of the pandemic and the challenges posed by new viral variants emphasize the importance of monitoring potential viral mutants and isolating high-risk populations to minimize mutational invasion (Gupta et al. 2023).

The emergence of new viral variants, particularly those of the Omicron lineage, has raised significant concerns regarding the neutralizing efficacy of monoclonal antibodies. Due to the reduced effectiveness against the predominant Omicron variant, the FDA has revised its approval for several monoclonal antibodies, noting that they did not meet the expected therapeutic outcomes. Monoclonal antibodies are not currently indicated for the treatment of acute COVID-19 infection, although some may still be authorized under emergency use conditions. As of January 2023, none of the

approved therapeutic monoclonal antibodies have demonstrated effective neutralization against the most widely circulating variants and subvariants, prompting the FDA and the North American National Institutes of Health (NIH) to recommend halting their use pending further evaluation. Currently, the monoclonal antibody Tixagevimab, when used in combination with Cilgavimab, is only indicated for pre-exposure prophylaxis (Brobst and Borger 2023).

Monoclonal antibody treatment and the opportunity to provide protective immunity

Monoclonal antibody therapy, by nature, is a form of passive immunotherapy that aims to control viral infections through direct and rapid action against the viral agent, rather than triggering a long-term immune response. This approach contrasts with vaccines, whose goal is to stimulate endogenous immunity, thus providing long-lasting protective immunity. Recent studies, however, have shown that monoclonal antibodies could serve as triggers for endogenous immune responses, producing vaccine-like effects that lead to prolonged immune responses. During immunotherapy, antiviral monoclonal antibodies form immune complexes with various cells, including infected ones. These complexes are recognized by antigen-presenting cells (APCs), which play a central role in acquired immunity. Surprisingly, until recently, the scientific community had not fully considered the potential of these complexes to activate the immune system, including the induction of humoral immune responses or cytotoxic T-cell responses. These effects are immunomodulatory and vaccine-like, enhancing the patient's defense against viral infections and potentially facilitating quicker recovery and shorter treatment durations. Therefore, it is entirely plausible to argue that monoclonal antibody treatment could stimulate the patient's immune system, activating both cellular and humoral immune responses in a way that provides protective immunity (vaccine-like effect) (Pelegrin et al. 2015).

Conclusion

The monoclonal antibodies offer a great therapeutic potential not only for the oncological diseases, where their use is well established. This class of therapeutics is of great importance for infectious diseases and, most of all, for the new, emerging, and widespread viral infections like COVID-19, which showed humanity that the world could be turned upside down in only a few months. The monoclonal antibodies are not only one more "weapon" in the existing therapeutic arsenal, but their use should be more deeply investigated because of their potential not only to cure, but to modulate the immune response of the patient in a long-lasting way.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

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Data availability

All of the data that support the findings of this study are available in the main text.

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