REVIEW ARTICLE

Monoclonal antibodies: a remedial approach to prevent SARS-CoV-2 infection

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Abstract

SARS-CoV-2, the newly emerged virus of the Coronaviridae family is causing havoc worldwide. The novel coronavirus 2019 was first reported in Wuhan, China marked as the third highly infectious pathogenic virus of the twenty-first century. The typical manifestations of COVID-19 include cough, sore throat, fever, fatigue, loss of sense of taste and difficulties in breathing. Large numbers of SARS-CoV-2 infected patients have mild to moderate symptoms, however severe and life-threatening cases occur in about 5–10% of infections with an approximately 2% mortality rate. For the treatment of SARS-CoV-2, the use of neutralizing monoclonal antibodies (mAbs) could be one approach. The receptor binding domain (RBD) and N-terminal domain (NTD) situated on the peak of the spike protein (S-Protein) of SARS-CoV-2 are immunogenic in nature, therefore, can be targeted by neutralizing monoclonal antibodies. Several bioinformatics approaches highlight the identification of novel SARS-CoV-2 epitopes which can be targeted for the development of COVID-19 therapeutics. Here we present a summary of neutralizing mAbs isolated from COVID-19 infected patients which are anticipated to be a better therapeutic alternative against SARS-CoV-2. However, provided the vast escalation of the disease worldwide affecting people from all strata, affording expensive mAb therapy will not be feasible. Hence other strategies are also being employed to find suitable vaccine candidates and antivirals against SARS-CoV-2 that can be made easily available to the population.

Keywords SARS-CoV-2 · Coronaviridae · COVID-19 · mAbs · Spike protein · Therapeutic

Introduction

Novel coronavirus 2019, named SARS-CoV-2 (Severe Acute Respiratory Syndrome- Coronavirus-2) by ICTV (International Committee on Taxonomy of Viruses) was first identified in Wuhan, China in late 2019 and since then it has caused worldwide pandemic by rapidly spreading into nations, affecting almost all developing as well as developed countries (Wang et al. 2020a, b). SARS-CoV-2 belongs to the family *Coronaviridae*, affecting mainly avian and mammalian species (Amirfakhryan and Safari 2021; Jahanshahlu and Rezaei 2020). Coronavirus outbreak was first identified in 2003 as an acute respiratory syndrome (Bhattacharya et al. 2021; Coughlin and Prabhakar 2012). Since then, it has resulted in a large number of infections ranging from mild respiratory problems to the Severe Acute Respiratory Syndrome (SARS) epidemic in 2003 and the Middle East Respiratory Syndrome (MERS) outbreak in 2012. Patients having SARS-CoV-2 infection may experience atypical pneumonia such as fever, cough, sneezing, muscle ache, asphyxia, loss or impairment of taste sensation, and loss of smell to severe lung damage accompanied by acute respiratory distress syndrome (ADRS) (Larsen et al. 2020). It was hypothesized that vectors of SARS-CoV-2 were bats and civets (Basson et al. 2011; Bindoli et al. 2020; Bournazos et al. 2020; Hamadi et al. 2020). Currently, SARS-CoV-2 is becoming more dangerous due to the continuous emergence of mutated strains which sometimes lead to an increased rate of infectivity, morbidity and mortality. Cardiovascular and hyperglycaemic patients are more prone to SARS-CoV-2 infection, hence preliminary screening and treatment are essential as cardiovascular diseases are the major cause of death worldwide (Lim et al. 2021; Shanmugaraj et al.

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2020; Wu et al. 2020a, b). Spike epitopes of the virus are responsible for causing brain inflammation by disrupting blood–brain barrier and infecting glial cells as confirmed by docking studies in which spike epitope peptides, M1Lys60 and Ala240Glu300, formed heterodimeric complex with TLR-8, VCAM1 proteins, zonula occludens and glial cell-specific protein NDRG2 and Apo-S100B (Dasgupta and Bandyopadhyay 2021). US-FDA (United States-Food and Drug Administration) and WHO (World Health Organisation) have permitted emergency use authorization of monoclonal antibodies (mAbs) such as etesivimab, bamlanivimab, and sotrovimab as prophylaxis or treatment for SARS-CoV-2 infection, but these mAbs have some limitations. Failure of WHO and FDA recommended mAbs for the therapy of novel strains of SARS-CoV-2 along with less efficacy of marketed vaccines provides a need to explore alternative therapeutic approaches (Chen et al. 2020a, b). This review article gives a brief description of neutralizing mAbs that have the potency to neutralize the coronavirus variants, SARS-CoV and SARS-CoV-2 in vitro primarily by targeting the trimeric spike protein which helps in the entry of the virus into host cells through the ACE2 (Angiotensin Converting Enzyme 2) receptors (Wrapp et al. 2020a, b).

Structure of SARS-CoV-2

Based on genomic sequencing data of SARS-CoV-2, it was found that the SARS-CoV-2 genome contains 29,891 nucleotides which encode both structural and non-structural proteins. Two third of its genome is enzymatically cleaved into sixteen putative non-structural proteins and four structural proteins such as S-protein (spike protein), M-protein (membrane protein), E-protein (envelope protein) and N-protein (nucleocapsid protein) encoded by 3′ end of the viral genome (Fig. 1) (Chen et al. 2020a, b; Jahanshahlu and Rezaei 2020). SARS-CoV-2 enters into the cytoplasm of the host cell through endocytosis using their densely glycosylated trimeric S-protein after attachment with the host cell ACE2 receptor (Chen et al. 2020a, b; Shanmugaraj et al. 2020; Wrapp et al. 2020a, b). S1 and S2 are the two functional subunits of SARS-CoV-2 S-protein that is responsible for cell attachment and membrane fusion respectively. S1 subunit has four core domains, S1A, S1B, S1C and S1D made up with 15–680 amino acids (AA) while the S2 subunit consists of 681–1255 AA. Spike glycoprotein is synthesized as a precursor molecule of approx. 180 kDa molecular weight while oligomerization and budding of virions occur in the endoplasmic reticulum and in pre-Golgi compartments (Ingallinella et al. 2004). On the basis of gene sequencing, it was found that there is a 77.5% similarity between SARS-CoV and SARS-CoV-2 (Coughlin and Prabhakar 2011; Jahanshahlu and Rezaei 2020). NTD (N-terminal domain) and CTD (C-terminal domain) are the two functional subunits
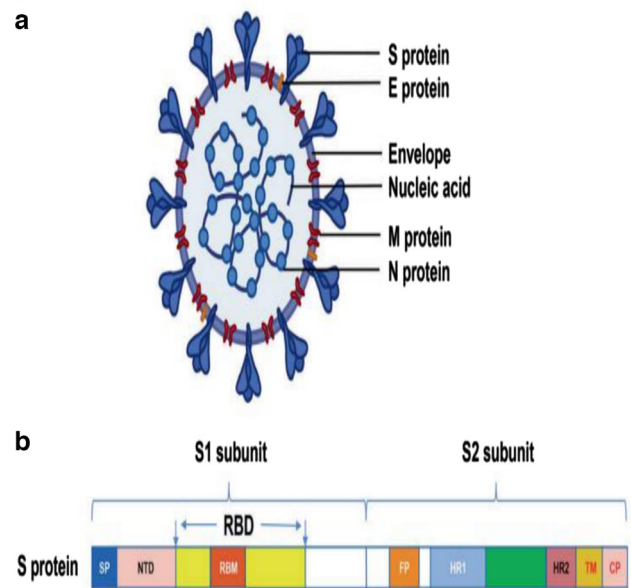
Fig. 1 Schematic diagram of SARS-CoV-2 particle and spike protein gene partitioning: **a** SARS-CoV-2 virus particle consists of S-protein (spike protein), M-protein (Membrane protein), N-protein (Nucleocapsid-protein) and E-protein (Envelope-protein). **b** The spike protein consists of two subunits S1 and S2 subunit, S1 subunit is again subdivided into SP (signal peptide), NTD (N-terminal domain), RBD (receptor binding domain), RBD contain RBM (receptor binding motif), FP (fusion peptide), HR1 (heptad repeat region1), HR2 (heptad repeat region2), transmembrane region (TM), and cytoplasmic tail (CP), which exhibits different function. (Yu F. 2020)

of SARS-CoV-2 spike protein (Cao 2020; Seydoux et al. 2020a, b). Receptor binding domain (RBD) of the S1 subunit consists of 193AA (residues 318–510) in which five cysteine residues are responsible for the expression and formation of RBDs. S-protein expression requires glycosylation of at least one site among residues 318, 330 and 357 of RBD. RBDs have a concave surface known as receptor binding motif (RBM) that attaches to the tip of ACE2 (Coughlin and Prabhakar 2011). RBDs of the S1 subunit shows hinge-like conformation, either one RBD in the "up" or "open" conformation which leads to a receptor accessible state (probably less stable conformational state) or all RBDs in the "down" or "closed" conformation leading to receptor inaccessible state (Seydoux et al. 2020a; Wrapp et al. 2020a, b). The S2 domain which is functionally important for fusion with cell membrane consists of two hydrophobic heptad repeats known as helical region (HR) and putative fusion peptide. HR1 (HR-N) and HR2 (HR-C) are combined together to form coiled-like structures which upon cleavage with the assistance of an endosomal protease cathepsin L enzyme, forms a 6-helix bundle fusion core which is separated by an interhelical domain made up with ~ 140 amino acids (Coughlin and Prabhakar 2011; Ingallinella et al. 2004). Although the function of NTD in SARS-CoV-2 is

unknown, employing sialosides as an alternative receptor for SARS-CoV-2 infection showed that NTD probably play a key role for its infectivity (Seydoux et al. 2020a, b). RBD of S1 undergoes a high rate of mutation causing failure of antibody-mediated neutralization without losing its infectivity, while the S2 domain is highly preserved amidst different clinical variants of SARS-CoV (Elshabrawy et al. 2012).

Receptor mediated entry of SARS-CoV-2

The ingress of coronaviruses into lung epithelial cells involves two steps, attachment with ACE2 receptor and membrane fusion. Similar to SARS-CoV, SARS-CoV-2 also utilizes CTD of RBD for entering into the host cells, however, some beta coronaviruses such as the HCoV-0C43 and HCoV-HKV1 bind with NTD of glycosylated cell surface receptor by recognizing 9-O-acetylated sialic acid moieties (Noy-Porat et al. 2021; Shanmugaraj et al. 2020). SARS-CoV-2 has 10–20 times higher affinity for ACE2 receptors as compared to SARS-CoV (Wrapp et al. 2020a, b). In the

membrane fusion step, SARS-CoV-2 S2-fusion protein shows three different states upon viral entry, the native state in which both subunits of spike protein remain connected to each other, the intermediate state in which the NTD of S1 is dissociated to expose their FP-region (fusion peptide region) and lastly the formation of fusion active state or collapsed 6-helix bundle, where both the viral and cellular membranes come together causing fusion with the host cell membrane and provide a passage to release the viral nucleocapsid into host cells (Fig. 2) (Ingallinella et al. 2004). After attachment of S1 subunit, S-protein is cleaved proteolytically by several host proteolytic enzymes such as furin, TMPRSS2 (transmembrane serine protease 2) and cathepsin-L. The active form of the S2 subunit is cleaved which allows viral-host membrane fusion leading to the entry of viral capsid into the host cell via endocytosis and release of viral RNA into the host cell cytosol. A number of auxiliary membrane proteins, in addition to the ACE2 receptor, have been linked to SARS-CoV-2 entry and transmission (Fig. 3). These proteins include CD147, NRP-1, Integrin, CD26, AGTR2, Band3,
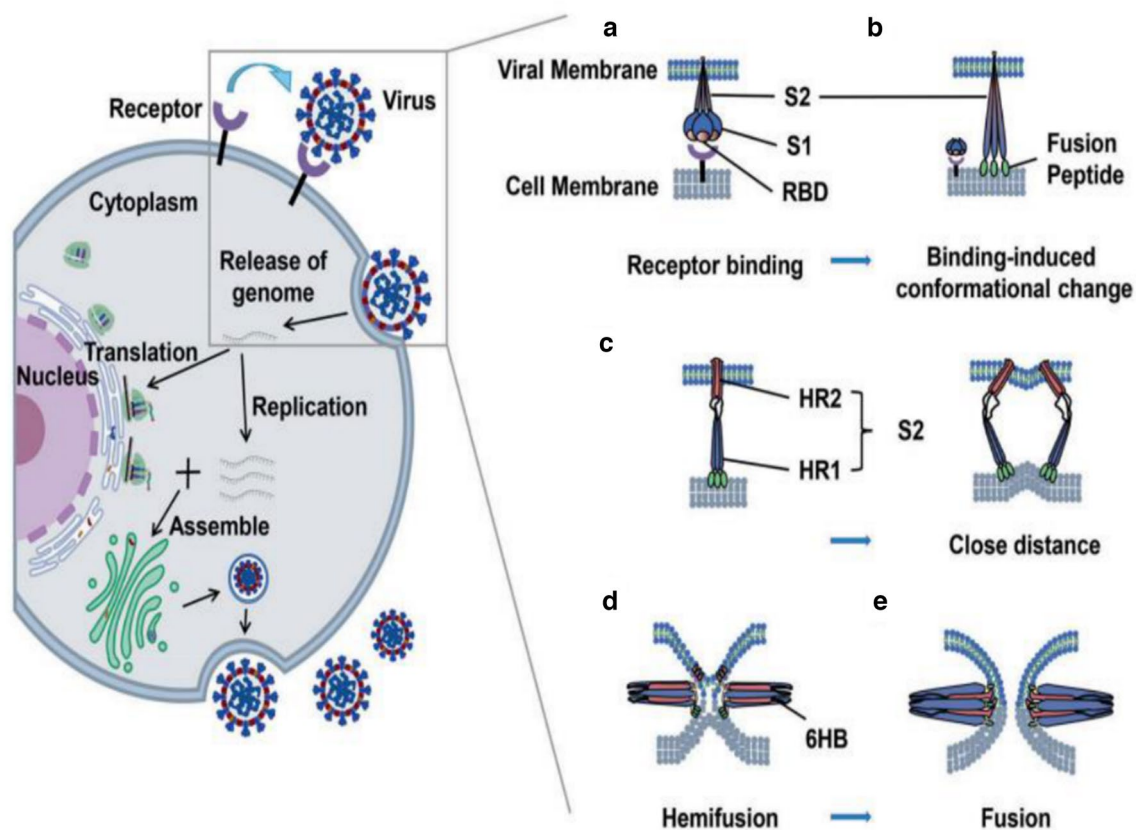
Fig. 2 Schematic diagram of SARS-CoV-2 life cycle. The coronavirus enters the host cell cytoplasm after binding with hACE2 receptor. **a** Spike protein of coronavirus recognise and attach with host cell hACE2 receptor; **b** After binding, conformational changes occur in the spike protein, leading to exposure of fusion peptide and fusion with the host cell membrane; **c** Both Heptad repeats of S2 subunit (HR1 and HR2) attract to each other to make the close distance between envelop protein of SARS-CoV-2 and host cell membrane; **d, e** HR1 and HR2 forms a 6-helix bundle (6-HB) that causes the virus envelope and host cell membrane to alter from hemifusion form to complete fusion, releasing the viral gene. (Yu et al. 2020a, b)
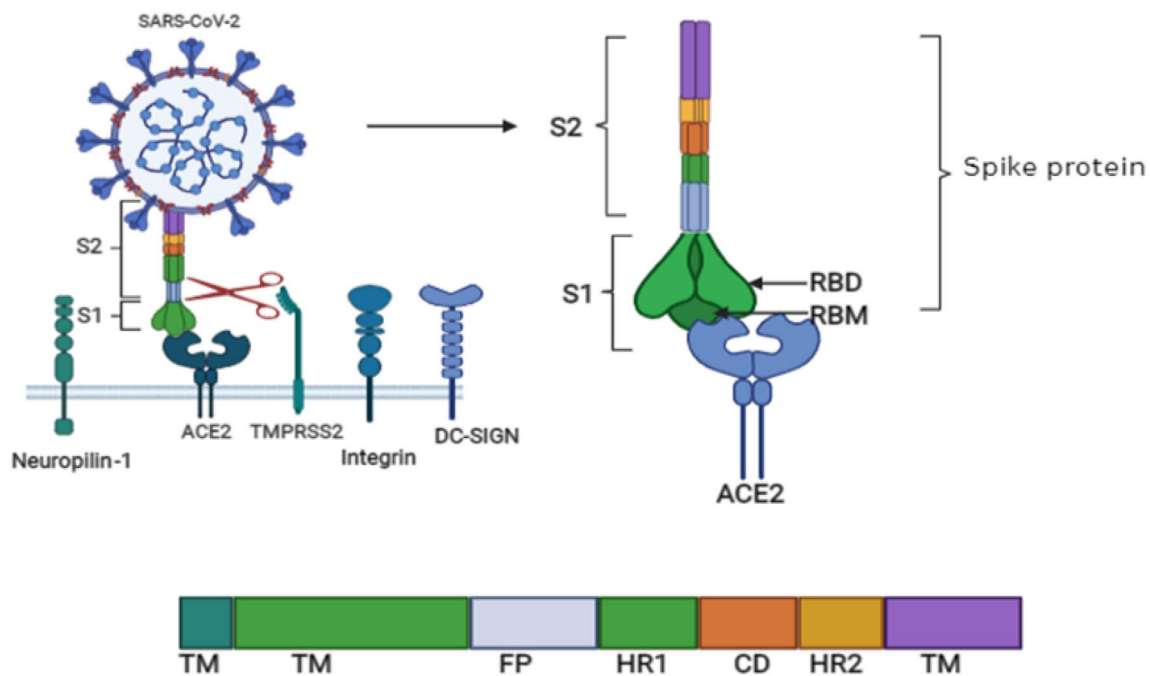
Fig. 3 Schematic diagram illustrating SARS-CoV-2 RBD binding with ACE2 receptor. S1 subunit of S-protein consists of RBD and RBM as main interacting sites. SARS-CoV-2 has a high affinity for ACE2 receptors as well as with other auxillary receptors such as neu-ropilin-1, integrin and DC-SIGN. Upon attachment, the S2 subunit is cleaved by host cell protease (TMPRSS2) facilitating fusion with the host cell membrane and insertion of genetic material into the host cell cytoplasm

KREMEN1, ASGR1, ANP, TMEM30A, TMPRSS2, and Furin (Alipoor and Mirsaeidi 2022). Basigin, also known as CD147, is a transmembrane protein that is highly expressed in the heart, kidneys, and lungs. It is a member of the immunoglobulin superfamily and is involved in the activation of T lymphocytes, the development of tumours, *Plasmodium* invasion, bacterial and viral infections, as well as playing a significant role in the entry of SARS-CoV-2 with the help of the RBD of S-protein (Wang et al. 2020). A transmembrane protein called neuropilin-1 (NRP-1) that is highly expressed in the endothelial and epithelial cells of the respiratory and olfactory systems serves as an entry point for a few numbers of viruses, including Epstein–Barr virus (EBV), human T lymphotropic virus type 1 (HTLV-1), and SARS-CoV-2. When the host furin cleaves the S-protein, the C-terminal motif is revealed, and C-end rule (CendR) attaches to the extracellular domain of NRP-1 before being endocytosed into the host cells (Daly et al. 2020). Dipeptidyl peptidase 4 (DPP4), also known as CD26, is a type 2 transmembrane glycoprotein that is extensively expressed in the kidney, leukocytes, and lungs. It is responsible for the proteolytic cleavage and activation of a variety of substrates, which controls and activates the immune response. Coronaviruses including SARS-CoV-1, MERS, and SARS-CoV-2 require CD26 to infect a variety of human cells (Vankadari et al. 2020). Integrins are transmembrane proteins that play diverse roles in cellular processes, such as cell adhesion, migration, and communication. They also serve as an alternative receptor for a number of viruses, including adenovirus, herpes simplex virus-2, human papillomavirus-16, and SARS-CoV-2. SARS CoV-2 entered host cells by binding with the integrin receptor via its conserved RBD motif (found in RBD of S-protein) (Sigrist et al. 2020). Angiotensin 2 receptor type 2 (AGTR2), which has a higher affinity with spike protein than ACE2, may serve as a possible receptor for SARS-CoV-2 (Cui et al. 2020).It is a known fact that the number of cleaved spike protein units is proportional to the infectivity of the virus, hence the SARS-CoV-2 mutant having a higher amount of cleaved spike proteins are highly contagious (Falcone et al. 2021; Mlcochova et al. 2021). By means of host cell machinery and genetic material, the viral components are produced followed by assembling of viral particles and release by exocytosis, mediating further infection to other healthy cells (Fig. 4) (Daniloski et al. 2021). HR-N and HR-C remain arranged in antiparallel way to independently form α-helical coiled structure in the spike protein (Ingallinella et al. 2004). The core of the SARS-CoV-2 RBD is a twisted five-stranded antiparallel sheet (β1, β2, β3, β4 and β7), which is connected by short helices and loops. There is an extended insertion encompassing the short β5 and β6 strands, α4 and α5 helices, and loops between the β4 and β7 strands in the core (Darwish 2021). Three of these four pairs—Cys336-Cys361, Cys379-Cys432 and Cys391-Cys525—are in the core and help in stabilising the β sheet
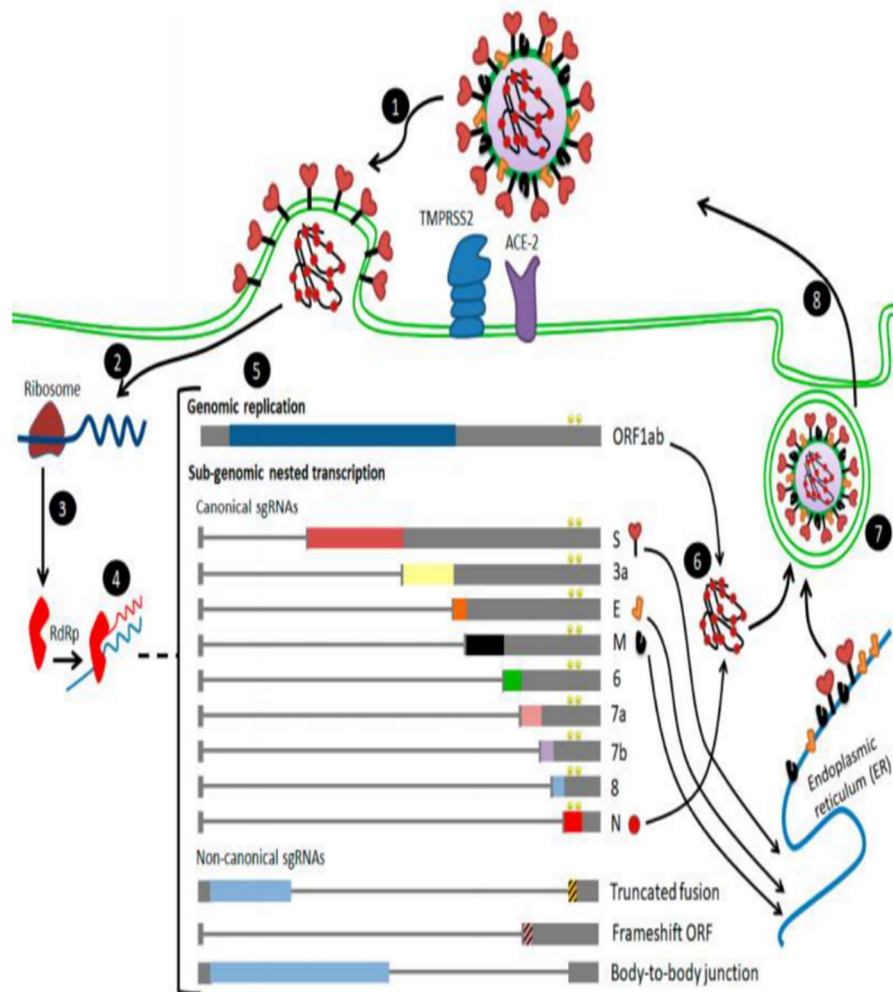
Fig. 4 Steps involved in SARS-CoV-2 infection and entry into the host cell cytoplasm. (1). After binding with ACE2 receptor, SARS-CoV-2 spike protein is cleaved proteolytically by TMPRSS2 (transmembrane protease serine2) enzyme and after fusion with host cells membranes, enters into the host cell. (2) With the help of two open reading frames ORF1a and ORF1b, genomic RNA of SARS-CoV-2 translate to form non-structural protein. (3) nsp12 gene is responsible for the production of non-structural proteins which have RNA-dependent RNA polymerase (RdRp) activity. (4) Positive-sense genomic RNA (gRNA) is synthesised from negative-sense RNA intermediates as the templates and the sub-genomic RNAs (sgRNA). The gRNA is packed by structural protein and convert into virion proteins to assemble progeny virions. Structural proteins (S, E, M and N), and several accessory proteins of SARS-CoV-2 are encoded by shorter sub-genomic RNAs. At least six auxiliary proteins (3a, 6, 7a, 7b, 8, and 10) have been identified in SARS-CoV-2, and non-canonical sgRNAs are also depicted in the picture (7,8); (7,8). The virus undergoes budding and exocytosis (Hatmal and Alshaer 2020)

structure. The remaining pair (Cys480-Cys488) joins the loops at the RBM's distal end. The peptide substrate binding site is formed between the two lobes of ACE2's N-terminal peptidase domain (Shah and Niaz 2021). The SARS-CoV-2 RBD's extended RBM interacts with the small lobe of ACE2 on its bottom side, and the RBM's concave outer surface allows for the N-terminal helix of ACE2 to fit properly against it (Lan et al. 2020). When the 614th amino acid in S-protein is mutated (D614G), the S1 and S2 subunits become more stable and the amount of functional S-protein on the viral surface increases. The S-protein of SARS-CoV-2 has so far been shown to have more than 1800 mutations

(including multiple mutations at the same locations), 235 of which have accumulated in the RBD (Padhi andTripathi 2020). Due to improved structural stabilisation of the RBD beta-sheet scaffold, the mutant type V367F that is persistently circulating around the world exhibited increased binding affinity to human ACE2. Phylogenetic analyses of the V367F mutants' genomes showed that the majority of V367F mutants are clustered more closely with the SARS-CoV-2 prototype strain during the early transmission phase than the dual-mutation variants (V367F + D614G) (Ou et al. 2020). Another study showed the functional impact of spike mutations, N-terminal domain (NTD)-specific E156G/Δ157-158

decreased susceptibility to vaccine-induced antibodies and increased infectivity (Mishra et al. 2022). Spike protein mutation at D614G leads to increased viral load, virulence and mortality by SARS-CoV-2 (Ogawa et al. 2020; Plante et al. 2021; Volz et al. 2021). D614G mutated pseudovirus show ~9 and ~eightfold high affinity to hACE2 and human lung epithelial cells than wild type SARS-CoV-2 respectively (Daniloski et al. 2020; Zhang et al. 2020). SARS-CoV-2 enters epithelial lung cells and releases their RNA that detects endosomal toll-like receptors (TLR3, TLR7, TLR8, TLR9), RIG1 (retinoic acid-inducible gene 1), MDA5 (melanoma differentiation-associated gene5), and nucleotidyltransferasecGAS (cyclic GMP-AMP synthase) in the cytoplasm. After the association between SARS-CoV-2 and alveolar cells, a downstream signalling pathway is initiated via TIR-domain-containing adaptor inducing interferon (TRIF) and stimulator of interferon genes (STING) adaptor molecules, leading to activation of NF-κB and interferon regulatory factor-3 (IRF3). This results in stimulation of pro-inflammatory mediator production including interferons (IFN-α, IFN-β, IFN-γ), interleukins (IL-1, IL-2, IL-4, IL7, IL-10, IL-12, IL-13, IL-17), TNF-α (tumour necrosis factor-α), macrophage inflammatory protein1α (MIP-1α), interferon-inducible protein-10, granulocyte stimulating factor, monocyte chemo-attractant protein1, monocyte stimulating factor and hepatocyte growth factor (HGF) which leads to lungs damage in COVID-19 patients (Kumar 2020; Soy et al. 2020; Ragab et al. 2020). According to different studies, it was shown that the number of lymphocytes including CD4+, CD8+ T-lymphocyte, and NK-cells, are remarkably reduced in patients having a serious illness of SARS-CoV-2 (Bindoli et al. 2020; Mansourabadi et al. 2020).

SARS-CoV-2 can also recognize C-type lectin protein receptors as glycan-dependent binding partners of the SARS-CoV-2 S-protein, C-type lectins (such as DC-SIGN, L-SIGN, LSECtin, ASGR1, and CLEC10A) bind to the RBD's extracellular regions. In contrary to supporting SARS-CoV-2's replication, engagement of these receptors with S-protein led to virus fusion and a strong proinflammatory response, which in turn caused lung inflammation and the cytokine release syndrome (Lu et al. 2021). C-type lectin proteins are highly expressed on immune cells, including monocyte, macrophages and dendritic cells which were implicated in SARS-CoV-2 pathogenesis. Due to the availability of an extra hACE2 binding site, SARS-CoV-2 can infect the lung as well as heart, intestine, and kidneys thus providing an alternative infection route (Mokhtari et al. 2020; Noy-Porat et al. 2021; Thierry and Roch 2020). The mAbs that target epitopes outside the RBM, such S309 and S2X333, exhibit a significant neutralising effect against infection that is facilitated by lectins (Lempp et al. 2021).

Recently, computational studies established two novel epitopes, RDLPQGFSA and FCLEASFNY, on SARS-CoV-2

binding to major histocompatibility molecules class I (MHC-I) and T-cell receptors. These epitopes were found to show high antigenicity response and docking score, thus making them suitable for vaccine development (Awad et al. 2022). Similar immunoinformatics approach identified 4 cytotoxic T-lymphocyte epitopes, GTDLEGNFY, TVNVLAWLY, GSVGFNIDY and QTFSVLACY, having an antigenic site and can be devised as a vaccine target (Waqas et al. 2021).

Monoclonal antibodies as a therapeutically active agent against SARS-CoV-2

The role of monoclonal antibodies as prophylaxis and alternative treatment strategy has been well established for immune-compromised patients affected with HIV-1 and respiratory syncytial virus (RSV) (Anderson et al. 2017; Xiao and Dimitrov 2007). Similarly, the utilization of mAbs against SARS-CoV-2 is being speculated. Screening data reported that few human monoclonal antibodies were found targeting SARS-CoV-2 RBD in immunized mice, rabbits and non-human primates (NHP) in the following ways (Muyldermans 2021; Wrapp et al. 2020a, b).

1. mAbs binds with RBD and interferes binding of the viral RBD to the ACE2 receptor in the following ways-
   - Monoclonal antibodies bind with the receptor binding motif (RBM) of RBD which functionally mimics ACE2 and blocks ACE2-RBD-binding.
   - Monoclonal antibodies attach to an epitope on RBD and disrupt ACE2-RBD binding indirectly.
   - Monoclonal antibodies partially bind with epitope present on RBD and mask the binding site which indirectly inhibits ACE2-RBD binding.
2. Prevents the release of viral nucleic acid outside of the cells- via neutralization, opsonization and complement activation by simulation of antibody constant region (Fc).
3. Antibodies bind to viral attachment proteins or cellular receptors, preventing them from attaching and entering the cell (Coughlin and Prabhakar 2011; Hassan et al. 2020).

Human mAb targeting SARS-CoV-2

In silico approach determines the binding ability of mAbs with different mutant variations of the virus. Molecular docking studies were performed by Das et al. using eight mAbs with in silico modified Fab region that were checked for their binding abilities with different lineages of SARS-CoV-2 B.1.1.7 and B.1.617.2 variant. Their results revealed the neutralizing capacity of cilgavimab, regdanivimab and tixagevimab were highest for Alpha lineages while the same was highest for bamlanivimab, sotrovimab and tixagevimab

in Delta lineages. Combination of these findings led them to design a chimeric antibody by conjugating CDRH3 of reg-danivimab on sotrovimab skeleton that could combat against escape mutants (Das et al. 2021). Similar docking studies performed by analysing docking energies of natural compounds with S-protein of virus and ACE2 receptor of host cell indicate quercetin 3-O-rutinoside-7-O-glucoside and neohesperidin having strong ligand–protein affinity (Shamkh and Pratiwi 2021). Based on cryoelectron microscopy structural data of RBD and S-protein as well as the screening of memory B-cells using PBMC (Peripheral Blood Mononuclear Cells) collected from both SARS-CoV-2 and SARS-CoV infected individuals, few human monoclonal antibodies were identified which can be designated as possible treatment options for severe SARS-CoV-2 infection (Table 1) (Pinto et al. 2020).

47D11

It is a chimeric monoclonal antibody derived from the immunization of transgenic H2L2 mice (Jahanshahlu and Rezaei 2020; Wang et al. 2020). 47D11 was experimentally found to inhibit growth and infection of SARS-CoV-spike and SARS-CoV-2 spike pseudo type VSV with IC_{50} 0.19–0.57 μg/ml via targeting the S1B RBD of SARS-CoV-S and SARS-CoV-2-S in VeroE6 cells. The binding affinity of 47D11 to SARS-S_{ecto} is higher than SARS-2-S_{ecto}, while binding affinities for SARS-S1B are similar in both SARS-CoV-2 and SARS-CoV. 47D11 binds to a conserved epitope in the SARS-CoV-2-S1B domain, consisting of a core domain and a receptor binding subdomain looping out from the antiparallel beta-sheet core domain structure (Wang et al. 2020a, b). Hence 47D11 can be utilized for the detection of antigen, serological assays specifically targeting the SARS-CoV-2 and for clearance of virus from the body as well as preventing the healthy cells from further infection (Fedry et al. 2021). It may be utilised as a potential therapeutic agent in combination with other mAbs to treat serious illnesses of SARS-CoV-2 (Gavriatopoulou et al. 2020).

B38 and H4

These two neutralizing mAbs were obtained from plasma of SARS-CoV-2 infected patients, targeting the RBD of SARS-CoV-2 spike protein. B38 and H4 are competitive inhibitors of ACE2 for RBD of SARS-CoV-2 (Jahanshahlu and Rezaei 2020; Sun et al. 2021). Based on collected experimental data, with an IC_{50} value of 0.177 μg/ml, B38 was shown to be more effective in inhibiting viral infection than H4, which had an IC_{50} value of 0.896 μg/ml. Based on the competition assay it was found that B38 and H4 would be an ideal pair of neutralizing mAbs, as they avoid immune escape by

targeting distinct epitopes on the RBD of SARS-CoV-2 (Yu et al. 2020a, b).

AB1

Identified by bio-panning against the SARS-CoV S-protein RBD from phage-displayed technique, fluorescence labelled antigen binding (Fab), single chain variable fragment (scFv) and variable heavy-chain (VH) libraries, these mAbs blocks the RBD-ACE2 binding by competing with ACE2 (Zeng et al. 2020). AB1 have relatively less somatic mutations, therefore, ab1 IgG1 antibodies have greater potency in prophylaxis and therapeutic for SARS-CoV-2 infection.

CB6

CB6 was discovered in PBMCs from a COVID-19 convalescent patient utilising the SARS-CoV-2 S-protein recombinant RBD. This antibody binds to soluble SARS-CoV-2 RBD, but not with SARS-CoV and MERS RBD S-protein. Followed by binding, neutralization of pseudoviruses and active viruses occur by blocking the link between SARS-CoV-2 RBD and host ACE2 receptor and compete with interface residue. Furthermore, CB6 was found to show positive effects in prophylaxis and treatment in SARS-CoV-2 infected rhesus macaque model (Hansen J. 2020). Although CB6 possess the potential risk of antibody-dependent enhancement effect (ADEE), it can be eliminated by introducing two leucine to alanine substitutions at residues 234 and 235 (LALA mutation) of the Fc-regions (Shi R. 2020).

S303, S304, S309 and S315

Obtained from the PBMCs of SARS-CoV infected patients after the screening of memory B-cells, these mAbs show cross-neutralization activity with SARS-CoV-2 by binding at the nano to sub picomolar concentrations with both SARS-CoV and SARS-CoV-2. More specifically, the S309 IgG binds to SARS-CoV-2 $S1_B$ domain, while S309 Fab binds with both $S1_A$ and $S2_B$ domains (D'Amato et al. 2021). S309 neutralises SARS-CoV and SARS-CoV-2 pseudovirus (SARS-CoV-2-MLV) with similar potencies, whereas S303 neutralises only SARS-CoV-MLV. SARS-CoV-MLV and SARS-CoV-2-MLV are both slightly neutralised by S304 and S315, respectively (Pinto et al. 2020).

Single domain antibodies (sdAbs)

A fully synthesised humanised phage display library with recombinant SARS RBD yielded five sdAbs (1E2, 2F2, 3F11, 4D8, 5F8) which were found to possess antiviral activity against SARS-CoV-2 in vitro (Wu et al. 2017, 2020a, b). According to pseudotyped virus and live virus neutralization

Table 1 Neutralizing monoclonal antibodies against SARS-CoV-2

Sr.no	Name of the antibodies	Type	Source	Preparation	Target on S-protein	References
1	47D11	IgG	Chimeric antibody	Transgenic mice, Hybridoma technology	RBD	(Wang et al. 2020; Gavriatopoulou et al. 2020)
2	B38	IgG	Human	Peripheral blood of SARS-CoV2-infected patients	RBD	(Jahanshahlu and Rezaei 2020)
	H4	IgG	Human	Peripheral blood of SARS-CoV2-infected patients	RBD	(Jahanshahlu and Rezaei 2020)
3	AB1	IgG	Human	Phage displayed Fab, scFv& VH libraries	RBD	(Zeng et al. 2020)
4	CB6	IgG	Human	B cells of convalescent patients and PBMCs	RBD	(Shi et al. 2020)
5	S309	IgG	Human	Peripheral blood of SARS-infected patients	RBD	(Pinto et al. 2020; Klasse and Moore 2020)
6	3F11	sdAb	Human	Humanized phage display library	RBD	(Yu et al. 2020a, b)
7	REGN10989, REGN10987, REGN10933, REGN10934	IgG	Human	Transgenic mice, peripheral blood of SARS-CoV2 infected patients; next generation sequencing	RBD	(Hansen et al. 2020; Baum et al. 2020)
8	H014	IgG	Chimeric antibody	Animal immunized and phage display	RBD	(Lv et al. 2020)
9	COV2-2196 and COV2-2130	IgG	Human	Peripheral blood of convalescent patients	RBD	(Zost et al. 2020)
10	4A8 and 0304-3H3	IgG	Human	Peripheral blood of convalescent patients	NTD	(Chi et al. 2020)
11	CV1 CV30 CV35	IgG	Human	PBMCs	RBD	(Seydoux et al. 2020a, b)
12	BLN1 BLN2 BLN3 BLN10 BLN12 BLN14	IgG	Human	Phage display, scFv library	NTD	(Noy-Porat et al. 2021)
13	REGN-CoV2 and LY-CoV555	IgG	Human	Phage display library	RBD	(Cohen 2021; Chen et al. 2021)
14	CR3022	IgG	Human	Gene cloning, protein expression	RBD	(Tian et al. 2020a, b)
15	CT-P59	IgG	Human	Phage display	RBD	(Kim et al. 2021)
16	COVA1-18 and COVA2-15	IgG	Human	B cells of convalescent patients	RBD	(Brouwer et al. 2020)
17	2A-Fc 1B-Fc	IgG	Llama	VHH-library	RBD	(Dong et al. 2020)
18	311mab-31B5 and 311mab-32D4	IgG	Human	B cells of convalescent patients	RBD	(Chen et al. 2020a, b)
19	CC12.1	IgG	Human	B cells of convalescent patients	RBD	(Yu et al. 2020a, b)
20	ADI-55689, ADI-55993, ADI-56000, ADI-55688, ADI-56046, ADI-56010, ADI-55690, ADI-55951	IgG	Human	Memory B cells of convalescent SARS donor	RBD	(Wec et al. 2020)

assay reports, these sdAbs show inhibitory action with an IC_{50} of 0.0038 μg/ml and 0.4360 μg/ml respectively. SARS-CoV-2 RBD and ACE2 binding is totally blocked by 3F11, whose neutralizing activity can be enhanced by fusion with human IgG Fc fragment. By virtue of the naïve llama library by in vitro phage-display technology, several nanobodies were identified which bind to the RBD of SARS-CoV-2 S-protein showing neutralization activity. H11 is a tightly binding nanobody with $Kd_{50} < 1$ μM and it produces mature mutants, H11-D4 and H11-H4, which vary from H11 and with each other at five CDR3 residues. H11-H4 and H11-D4 bind to RBD with Kd_{50} of 5 nM and 10 nM respectively, and hence limit RBD binding to ACE2. The plaque reduction neutralisation test (PRNT) reported that H11-D4-Fc and H11-H4-Fc had Nd_{50} of 18 nM and 6 nM respectively, hence can neutralise live SARS-CoV-2 infection (Huo et al. 2020a). Combination of CR3022 with H11-H4-Fc or H11-D4-Fc displayed a synergistic neutralization effect (Yu et al. 2020a).

REGN10989, REGN10987, REGN10933, REGN10934, REGN10977, REGN10964, REGN10954, REGN10984 and REGN10986

Using transgenic mice and PBMCs of SARS-CoV-2 infected patients about 40 antibodies were screened from a single B-cell and among them 9 antibodies (REGN10989, REGN10987, REGN10933, REGN10934, REGN10977, REGN10964, REGN10954, REGN10984 and REGN10986) have been found to show strong neutralization potency against SARS-CoV-2 with IC_{50} value ranging from 7 to 99 pM (Tada et al. 2021). Sequencing of antibodies from the B-cells suggested that it produces large quantities of fully humanized antibodies which bind to the critical RBD of S-protein and become an ideal partner for therapeutic antibodies cocktail that decreases the potentiality of viral escape mutants (Hansen et al. 2020). Antibodies cocktail of REGN10987 and REGN10933 have the capability to avoid neutralization escape by binding to the distinct and non-overlapping regions of the RBD. In the presence of these antibodies VSV-SARS-CoV-2-S pseudovirus did not show the overgrowth of escape mutation (Baum et al. 2020). In addition, four antibodies (REGN10989, REGN10987, REGN10933, REGN10934) can productively lead to viral neutralization with IC_{50} values of 7.38 pM, 42.2 pM, 37.4 pM and 28 pM respectively. Clinical trials of cocktail antibodies are currently undergoing (Hansen et al. 2020; Yu et al. 2020a, b). Studies indicate that a cocktail of non-competitive antibody therapy can effectively evade viral escape mutation which is obligatory to combat various SARS-CoV-2 mutants (Baum et al. 2020; Yao et al. 2021).

H014

H014 is a humanized mAb obtained from RNA extract of mice peripheral lymphocyte after immunization with SARS-CoV spike protein by phage display library technology, which exhibit neutralization ability for both SARS-CoV and SARS-CoV-2 (Yao et al. 2021). Both H014 IgG and Fab fragments are found to exhibit a strong binding affinity for the viral receptor binding domain with remarkable binding affinities at sub-nM levels and shows a potent pseudovirus neutralizing activity with IC_{50} value of 3 nM and 1 nM against SARS-CoV-2 and SARS-CoV, respectively. H014 treated hACE2 humanized mice show a 10-100 fold reduction in viral titres (Lv et al. 2020). H014 is found to recognise a conformational epitope (present on the side of the open receptor binding domain and distinct from RBM) and inhibit the protein–protein interaction (Lv et al. 2020; Yu et al. 2020a, b).

CoV2-2196 and CoV2-2130

These neutralizing mAbs were obtained by screening the lymphocyte with SARS-CoV-2 S-protein from SARS-CoV-2 convalescent patients and were found to neutralize SARS-CoV-2 pseudovirus by binding with spike protein and inhibiting the interaction of RBD-hACE2. Both of these antibodies were reported to show a synergistic neutralizing effect against live SARS-CoV-2 infection (Zost et al. 2020).

4A8 and 0304-3H3

These neutralizing mAbs were screened out from B-cells of COVID-19 infected patients who exhibit high neutralization capacity with IC_{50} values of 0.61 and 0.04 μg/ml respectively. These mAbs did not recognise the RBD and were unable to disrupt the association between the ACE2 receptor and the SARS CoV-2 S-protein in vitro, but retained a strong neutralising efficacy against both real and pseudotyped SARS-CoV-2. Cryo-electron microscopy structure of S-protein and 4A8 revealed that three 4A8 Fab interact with one NTD of the S-protein to stabilize the NTD epitope and neutralize SARS-CoV-2 infection (Chi et al. 2020).

CV1, CV30 and CV35

These were isolated from SARS-CoV-2S-protein specific B-cells, which were obtained from serum and PBMCs of COVID-19 infected patient. CV1 and CV35 differ from each other by one synonymous LC-mutation. All these mAbs

bind to the stabilized SARS-CoV-2ectodomain spike protein. CV30 was found to be approximately 530 times more potent as compared to CV1 and CV35 (IC_{50}-0.03 μg/ml) and achieve 100% neutralization (Seydoux et al. 2020b).

BLN 1-BLN10, BLN12, and BLN14

These antibodies were isolated from B-cells of severely infected COVID-19 patients' phage-display-single-chain variable fragment (scFv) from the phage display library (Bobkov et al. 2018). Neutralization activity of these monoclonal antibodies were established by ELISA and PRNT (plaque reduction neutralization test). All these monoclonal antibodies exhibited high specificity for NTD with no affinity for RBD. Among them, BLN1 and BLN12 show the highest affinity while BLN4 shows the lowest. BLN1 and BLN12 are highly potent (IC_{50} value 8 ng/ml) while BLN8 is less potent (IC_{50} value 54.9 μg/ml). BLN12 and BLN14 have up to 80–100% and ~85% respectively neutralizing activity in K18-hACE2 transgenic murine model (Noy-Porat et al. 2021).

REGN-CoV2 and LY-CoV555

REGN-CoV-2 is a combination of casirivimab and imdevimab directed against the S-protein of SARS-CoV-2 in-patients with early infection (O'Brien et al. 2021; Weinreich DM 2021). Clinical trial data indicated that patients receiving either dose of LY-CoV555 or REGN-CoV-2 had lower SARS-CoV-2 spike-RNAs level than the placebo control group (Cohen 2021). Previously it was reported that LY-CoV555 show protection in non-human primates against SARS-CoV-2 by blocking the viral attachment to the cells thus preventing entry. A randomized trial data indicated that patients receiving LY-CoV555 had a viral load lower than the placebo control group (Chen et al. 2021; Falcone et al. 2021).

CR3022

This mAb was obtained from the convalescent blood of SARS-CoV infected patients and shows cross-neutralization activity against SARS-CoV-2 by potentially binding to SARS-CoV-2 RBD and inhibit the interaction between ACE2 and SARS-CoV-2, with a binding affinity (KD_{50}) of 6.3 nM (Tian et al. 2020a, b). CR3022 and CR3014 recognize different epitopes on RBD and neutralize the SARS-CoV in a synergistic fashion. Differences in RBD at the C-terminus residues between SARS-CoV-2 and SARS-CoV does not affect binding to ACE2 receptor as it completely neutralizes both the wild-type SARS-CoV and SARS-CoV-2

However, it has a significant impact on neutralising antibody cross-reactivity. m396 and CR3014 are some of the potent SARS-CoV specific neutralizing antibodies which target RBD of SARS-CoV-2 S-protein (Huo et al. 2020a, b; Tian et al. 2020a, b).

CT-P59

Obtained by phage display scFv method using RBD of SARS-CoV-2 S-protein and reformatted into human IgG, CT-P59 shows strong neutralization potential as evidenced by in vitro PRNT against SARS-CoV-2 wild type and D614G variant, with IC_{50} value of 5.7 ng/ml and Kd_{50} value of 27 pM. It inhibits SARS-CoV-2 infection via steric hindrance with ACE2 receptor and mitigate the infection both in vitro and in vivo (Kim et al. 2021).

COVA1-18 and COVA2-15

These mAbs were obtained from PBMCs of SARS-CoV-2 infected patients using SARS-CoV-2 S-protein as antigen. Both of these neutralizing monoclonal antibodies target the RBD of SARS-CoV-2 S-protein. In addition, they have neutralization activity for both pseudovirus and live virus of SARS-CoV-2with an IC_{50} value of 8 ng/ml and 7 ng/ml respectively (Brouwer et al. 2020).

2A-Fc, 1B-Fc and 3F-Fc

These mAbs were isolated from SARS-CoV-2 infected patient with the help of two llama VHH libraries (one naïve library and another humanized synthetic library) (Muyldermans 2021). 1B-Fc and 2A-Fc compete for the same S1 RBD epitope among which 2A-Fc has a stronger affinity, while 3F-Fc bind to a different epitope of S1 RBD and inhibits ACE2-RBD interaction of SARS-CoV-2. These antibodies are known as tri-specific antibodies as they bind to different epitopes and show strong neutralization activity. Tri-specific VHH-Fc-3F-1B-2A show higher affinity (KD_{50} value of ~0.047 nM) than bi-specific VHH-Fc-3F-1B and individual antibodies. In addition, tri-specific VHH-Fc-3F-1B-2A are highly potent for blocking the spike protein and ACE2 interaction with IC_{50} value of 0.71 nM, and full inhibition occurs around at 10 nM concentration. These mAbs have superiority if used in combination than using as a single component of VHH-Fc in which IC_{50} value is 2.21 nM and full inhibition occurs around 100 nM (Dong J. 2020).

311mab-31B5, 311mab-32D4 and 311mab-31B9

Isolated by cloning of VH and VL (variable light chain) regions of IgG from memory B-cells of COVID-19 infected patients.f, 311mab-31B5 and 311mab-32D4 have blocking

capacity for the SARS-CoV-2 RBD and hACE2 receptor interaction with an IC_{50} value of 33.2 ng/ml and 45 ng/ml respectively evidenced from the plasma test result, while 311mab-31B9 is unable to inhibit SARS-CoV-2 RBD-hACE2 interaction. Both 311mab-31B5 and 311mab-32D4 have neutralization activity for SARS-CoV-2 pseudovirus with an IC_{50} value of 33.8 and 69.8 ng/ml respectively, while no neutralization activity has been observed for 311mab-31B9 (Chen et al. 2020a, b).

CC12.1, CC6.29 and CC6.30

These monoclonal antibodies were obtained from the screening of the blood plasma of COVID-19 patients by using high throughput screening (HTS) with a specific antigen. CC12.1 was found to inhibit ACE2 binding with the RBD of SARS-CoV-2 and neutralization assay for the SARS-CoV-2 pseudovirus and protection assay using Syrian hamsters proved these mAbs to be antiviral with IC_{50} value of 0.019 μg/ml and 0.022 μg/ml respectively. In addition, CC6.29 and CC6.30 display the highest potency against SARS-CoV-2 with IC_{50} value of 2 ng/ml and 1 ng/ml by targeting the RBD of SARS-CoV-2 (Yu et al. 2020a, b).

ADI-55689, ADI-55993, ADI-56000, ADI-55688, ADI56046, ADI56010, ADI55690 and ADI-55951

These mAbs which were obtained from a convalescent SARS-CoV-2 donor using memory B-cells show cross-neutralization activity for both the SARS-CoV, SARS-CoV-2 and other SARS-like viruses. ADI55689 close the conserved core region of SARS-CoV-2 RBD epitope by binding to the margin of the ACE2 receptor, but ADI-56046 binds to the flexible tip. IgG format of these neutralizing mAbs can neutralize both SARS-CoV-2 live viruses and a VSV-based pseudovirus at 100 nM in neutralizing assay. ADI-55689 and ADI-56046 show neutralizing activity with IC_{50} value of 0.05–1.4 μg/ml and 0.004–0.06 μg/ml against SARS-CoV-2 and SARS-CoV, respectively. Similar IC_{50} values were observed in neutralization assays of SARS-CoV-2 and SARS-CoV live virus (Wec et al. 2020; Yu et al. 2020a, b).

AZD7442

It is a combination of two mAbs, tixagevimab (AZD8895) and cilgavimab (AZD1061), derived from B-cells of SARS-CoV-2 convalescent patients. These mAbs contain half-life extending modifications and binds to non-overlapping epitopes of the SARS-CoV-2 RBD (Mahase 2021). Prophylactic administration in the non-human primate model prevented infection whereas therapeutic administration was found to clear lung infection (Loo et al. 2022). Phase 1 trial of 300 mg intramuscular injection of AZD7442 revealed

increased virus neutralizing titres even after 9 months than convalescent serum. A double-blinded randomised placebo-controlled phase 3 trial proves intramuscular AZD7442 suitable as immunoprophylaxis to prevent COVID-19 in subjects having a poor response to COVID-19 vaccination (Levin et al. 2022).

The possible drawbacks of proposed mAb therapy

Antibodies mediated SARS pathogenesis

Scientific consideration is required to prove that neutralizing mAbs may contribute to SARS pathogenesis. SARS-CoV-2 infection or passive immunization in macaque models displayed production of spike protein-mediated IgG production, which was reported to exacerbate acute lung injury (ALI) by suppressing inflammation resolving response, abrogating wound healing, promoting MCP-1 (monocyte chemoattractant peptide-1) and IL-8 production and increasing pro-inflammatory monocytes and macrophages recruitment (Siddiqi et al. 2021). It was observed that patients deceased due to SARS-CoV-2 infection had stronger and faster neutralizing S-protein binding antibody responses than those who recovered. Subsequent analysis of sera from deceased patients has shown an increased level of IL-8 and SARS-CoV-2 induced MCP-1 produced by monocyte-derived wound healing macrophages. This suggests that there are possibilities in the enhancement of neutralizing antibody response, leading to the pathogenesis of SARS infection and disease propagation, due to the immune complex formation and macrophages infiltration. There were speculations of a link between sero-conversion and the rapid disease progression that happened in the second-week post first symptom appearance, but this is yet to be proven. Other report suggests that multiple coronavirus vaccine and anti-spike mediated antibodies have pathogenic effect in animal models, due to an increase in eosinophilia and pro-inflammatory pulmonary responses upon challenging the immunized animals. Influenza-A H1N1 pandemic in 2009 showed that antibodies against influenza antigen produced severe illness, but those antibodies were unable to neutralize influenza viruses and the resulting immune complex formulation caused a pathogenic trigger (Klasse and Moore 2020).

Antibody-dependent enhancement of infection (ADE)

ADE of infection can be there when the antibody occupancy on the virion-surface epitope falls below a critical threshold level, more precisely when inadequate antibodies occupy the viral epitope as found in the case of alpha virus and flavivirus (Dengue virus and Zikavirus) (Lee et al. 2020a, b; Tirado and Yoon 2003). ADE is an Fc-receptor-dependent phenomenon. On the contrary, non-neutralizing antibodies

which bind to an antigenic epitope of virion surface and not mediate entry may also confer ADE (Shukla et al. 2020). In vivo observation of ADE is an unacceptable result of recent Dengue vaccine (Dengvaxia) trials which resulted in critical disease condition in seronegative children (Shukla et al. 2020). Patients with COVID-19 were reported that higher antibodies titres against SARS-CoV-2 being associated with more severe disease (Lee et al. 2020a, b; Tirado and Yoon 2003). In the case of COVID-19, ADE can occur at sub-therapeutic levels of antibodies, incomplete vaccination or due to less efficacious antibodies obtained from plasma (Klasse and Moore 2020; Lee et al. 2020a, b). But to date, no clinical data could prove the occurrence of ADE from neutralizing mAbs monotherapy involving REGN-COV2, LY-CoV555 or bamlanivimab (Chen et al. 2021; Gottlieb et al. 2021; Weinreich et al. 2021).

Neutralizing antibodies mediated SARS-CoV2-S protein mutation

SARS-CoV-2 utilize their spike proteins for attachment with the host cell, so SARS-CoV-2 S-protein should be the primary target of neutralizing antibodies. However, some viruses like the influenza virus escape from the immune response by mutating their hemaglutinin (HA) and neuraminidase (NA) proteins (Chen et al. 2018). It is unclear whether SARS-CoV-2 will be able to mutate in the same manner to elude antibodies (Mlcochova et al. 2021). To establish neutralizing antibody-mediated SARS-CoV-2 mutation and antibody escape, a study was performed in which *ex vivo* human cells were infected with a spike protein containing the recombinant virus which were treated with neutralizing monoclonal antibodies obtained from either SARS-CoV-2 infected patients or manufactured antibodies. The results indicated that viruses with mutated spike protein were able to survive due to escape from antibodies and remained undetected (Örd et al. 2020).

Discussions

Coronaviruses with mutated spike proteins have the ability to escape from antibodies and are able to cause further infection. These types of mutants are already circulating in the human population, which are tagged as a variant of concern (VOC) by WHO (Mlcochova et al. 2021). Development or designing of vaccines which could be able to generate the strongest possible immune response and produce antibodies targeting more than one epitope of spike protein would be highly advantageous (Muyldermans 2021; Ning et al. 2021). Additionally, therapies based on antibodies should be used in combination which target at least two different sites on S-protein to prevent antibody resistance and are able to maintain the potency of

the vaccine and antibodies for long-term (Parray et al. 2020). Natural SARS-CoV-2 infection may be unable to produce a sufficient number of antibodies due to insufficient B-cells expansion and maturation. Sub-optimal concentration of neutralizing antibodies generated by vaccination or neutralizing antibody therapy leads to the generation of antibody-resistant SARS-CoV-2 mutants. Individuals with waning serological immunity or previously COVID-19 infected individuals are similarly prone to develop antibody escape variants (Weisblum et al. 2020). The Food and Drug Administration (FDA) granted Emergency Use Authorizations (EUAs) to bamlanivimab plus etesevimab, casirivimab plus imdevimab (REGEN-COV), and sotrovimab for the treatment of COVID-19. These mAbs are strictly restricted for patients with severe COVID-19 illness or those receiving oxygen therapy or supportive oxygen therapy with mechanical ventilation. In patients who received these mAbs, hypersensitivity including anaphylaxis and infusion-related events has been noted. There have also been reports of rash, diarrhoea, nausea, vomiting, and pruritis (Lanini et al. 2022). With the development of vaccines and other cutting-edge treatments, the epidemic has been largely under control. However, the emergence of SARS-CoV-2 variants linked to higher rates of human infection and transmission raises concerns because these vaccines and mAbs are still less effective against these variants than against the wild-type SARS-CoV-2. Drugs that can treat serious medical conditions and illnesses that arises due to SARS-CoV-2 are still urgently needed (Wang et al. 2021). Recently, according to the computational approach, the complex of hACE2 and S-protein of both SARS-CoV-2 and SARS-CoV were found to be most stable at pH 7.5–9 (Sharma and Deep 2020; Xie et al. 2022). Moreover, the patients having Burkitt's oesophagus and patients under a proton pump inhibitor regimen are more vulnerable to increased severity of infection due to higher expression of ACE2 receptor augmenting SARS-CoV-2 entry (Jimenez et al. 2021). Hence alternative prophylactic strategies are required to prevent infection in such vulnerable patients.

Thus mAb therapy should be considered only for candidates with a poor antiviral response such as geriatric or immunodeficient patients (Taylor et al. 2021). Several antiviral medications, including oseltamivir, lopinavir, ritonavir, ribavirin, remdesivir, favipiravir, hydroxychloroquine, corticosteroids, ascorbic acid, tocilizumab, azithromycin, and baricitinib, were used to treat COVID-19 patients. However, these medications have a number of side effects, which include anaemia, cardiac arrest, bradycardia, hypotension, diarrhoea, nausea, vomiting, dyslipidaemia and liver disease. Monoclonal antibodies on the other hand are well-tolerated with minimal side effects, therefore COVID-19 patients with such complications can be treated with mAbs such as bamlanivimab etesevimab, casirivimab imdevimab, and sotrovimab (Temsah et al. 2022).

Conclusion

The ongoing SARS-CoV-2 pandemic has created an emergency to discover prophylactic or therapeutic antiviral agents to mitigate COVID-19. Due to the high mutation rate in SARS-CoV-2 genome and the ability to escape from active as well as passive immune response it is important to generate highly conserved mAbs which can completely block the spike protein and inhibit the interaction with ACE2 receptor. SARS-CoV-2 has a higher mutation rate in their S-protein region, therefore, using single monoclonal antibodies could not be a wise decision, because it could accelerate the mutation and immune evasion. The promising result of neutralizing mAb cocktails as antibody therapy can provide an alternative way in the mitigation of future strains of SARS-CoV-2 as well in individuals having poor vaccine response. Since the disease has escalated at worldwide level affecting people from all economic strata, it is not feasible to provide expensive mAb therapy to the whole population. Hence emphasis should be laid on the search for a potent therapeutic antiviral medication which has the ability to cure and prevent SARS-CoV-2 infection successfully.

Declarations

Conflict of interest None to declare.

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