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The role of spike protein entry inhibitors in the treatment of mild-to-moderate covid-19 in nonhospitalized patients

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a deadly pneumonia caused by an enveloped, single-stranded positive-sense RNA (+ssRNA), 29.881 kb betacoronavirus, belonging to the coronaviridae 2B lineage.[1] Clinically, about 80% of the patients with Covid-19 develop asymptomatic or mild illness, usually within 12 days, whereas 15-30% progress to severe disease with acute respiratory distress syndrome (ARDS), hypoxaemic respiratory failure, multi-organ failure (MOF), and death.[2] Patients with mild or moderate SARD-CoV-2 are individuals who have respiratory symptoms but are not in respiratory distress, and have no multiorgan dysfunction, or other complications of Covid-19 that require hospitalization.[3] These patients can easily be treated as outpatients under quarantine. However, these individuals can progress to severe SARS-CoV-2 requiring hospitalization, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) if they are not treated. SARS-CoV-2 gain entry into host cells via its spike protein (S) which attaches to its cognitive receptor angiotensin-converting enzyme 2 (ACE2). Spike protein entry inhibitors (SPIs), such as bamlanivimab-etesevimab, casirivimab plus imdevimab, sotrovimab, and bebtelovimab have the potential to inhibit endocytosis, and replication of SARS-CoV-2 in host cells. However, the evolving mutations of SARS-CoV-2 has led to the emergency of new variants, such as Delta Plus, and Omicron BA.1, BA.1617, and BA.2 which are resistant to bamlanivimab-etesevimab, and casirivimab plus imdevimab. Henceforth, these doublet biologics are no longer used in many countries, including the USA. Sotrovimab and bebtelovimab are potent to most variants of concern, and BA.1, they are recommended for the treatment of non-hospitalized patients with Covid-19 in countries with high prevalence of Omicron BA. 1. However, sotrovimab has lost activity against BA.2, therefore, it is no longer recommended in all the states and territories in the USA. Currently, only bebtelovimab is the recommend SPI for the treatment of non-hospitalized patients in the USA.

Keywords: SARS-CoV-2, spike protein, spike protein inhibitors, sotrovimb, bebtelovimab

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a deadly pneumonia caused by an enveloped, single-stranded positive-sense RNA (+ssRNA), 29.9 kb betacoronavirus belonging to the coronaviridae 2B lineage.[1] Clinically, about 80% of the patients with Covid-19 develop asymptomatic or mild illness, usually within 12 days, whereas 15-30% progress to severe disease with acute respiratory distress syndrome (ARDS), hypoxaemic respiratory failure, myocardial injury, multi-organ failure (MOF), and death.[2]

Patients with mild or moderate SARD-CoV-2 develop mild respiratory symptoms but are not in respiratory distress, and have no multiorgan dysfunction (MOD), or other complications of Covid-19 that require hospitalization. These patients can easily be treated as outpatients under quarantine. However, these individuals can progress to severe SARS-CoV-2 requiring hospitalization, oxygen supplementation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) if they are not treated. Apparently, patients with mild-to moderate disease harbour Covid-19 viruses which are replicating in their nasal mucosa and lungs, and can transmit SARS-CoV-2 in the community.[3] Moreover, SARS-CoV-2 has high transmissibility during asymptomatic and mild disease.[4] Early treatment of Covid-19 in patients with mild-to-moderate disease can suppress progression of the disease, and prevent hospitalization and death; and is cost-effective. Furthermore, early treatment of SARS-CoV-2 can prevent transmission of the highly contagious disease.

SARS-CoV-2 is transmitted by fomite and air-droplets during close contact between infected and uninfected individual. SARS-CoV-2 can also be transmitted through direct contact transmission from contaminated hands which touch the mucosa of the nose, mouth, and conjunctivae. Covid-19 infection is usually through the nasal passages, but the virus can also gain access though the mouth, and conjunctivae, causing infection.[5] There is also a possibility that SARS-CoV-2 can be transmitted via the fecal-oral route in children.[6] and through transplacental vertical transmission in neonates.[7] Therefore, safe post-exposure treatment of expecting mothers is crucial to prevent congenital SARS-CoV-2, and congenital neurological disorders in neonates. Asymptomatic individuals and symptomatic patients are the main source of infection, and hospital acquired infections can occur in healthcare workers from patients or during medical procedures.

Covid-19 variants and mutations

SARS-CoV-2 is a very illusive virus which is capable of mutating over time, and evading host immunity. Since Covid-19 originated from Wuhan market selling solid animals, China in December 2019 there has been several mutations, such as Alpha B.1.1.7 (UK), Beta B.1.351 (South Africa), Delta B.1.617.2 (India), Omicron BA.1, BA.2, BA.2.12.1, BA.3, BA.4, BA.5, B.1.529 (nicknamed "Centaurus" [several countries]). These new mutated variants are associated with excessive proliferation and secretion of the Covid-19 viruses. In addition, these subvariants have a higher affinity for the ACE2 receptors.[8] and are possibly more contagious and easily transmissible.[8]

The mutations in the Covid-19 variants, particularly Omicron BA.1, BA.2, and BA.617.2 confer resistance to almost all the current biologics for the treatment of SARS-CoV-2.[9] Furthermore, infection with older variants of SARS-CoV-2, such as Omicron BA.1 does no confer immunity from infection with the new mutated sublineages of Omicron, including BA.1.12.1, BA.4, and BA.5.[10] These subvariants can even infect fully vaccinated individuals, including those who have received a third booster mRNA Covid-19 vaccine.

Unfortunately, thesemutation are here to stay, therefore, there is urgent need to develop new effective biologics which can overcome the evasion dirty tactics of SARS-CoV-2.

SARS-CoV-2 gain entry into host cells via its spike protein (S) which attaches to its cognitive receptor angiotensin-converting enzyme 2 (ACE2). Spike protein entry inhibitors (SPI) have the potential to inhibit entry, and replication of SARS-CoV-2 in host cells. They are the first host defence biologics against Covid-19, and have the potential for early treatment of mild-to-moderate SARS-CoV-2 in outpatients. There are several spike protein entry inhibitors which have been granted emergency use authorization (EUA) by the US Food and Drug Administration (FDA), such as bamlanivimab-etesevimab, casirivimab plus imdevimab, sotrovimab, and bebtelovimab. However, the evolving mutations of SARS-CoV-2 has led to the emergency of new variants, such as Delta Plus, and Omicron BA.1, BA.2, BA.2.12.1, BA.1617, BA.4, and BA-5 which are resistant to bamlanivimab-etesevimab, and casirivimab plus imdevimab. Henceforth, these doublet biologics are no longer used in many countries, including the USA. Sotrovimab and bebtelovimab are potent to most variants of concern (VOC), and BA.1, they are recommended for the treatment of non-hospitalized patients with Covid-19 in countries with high prevalence of Omicron BA. 1. However, sotrovimab has lost activity against BA.2, which account for about 50-70% of the infections in the USA, hence, it is no longer recommended in all the states, and territories in the USA.[11] Only bebtelovimab is the recommend SPI for the treatment of non-hospitalized patients in the USA.

Coronavirus 2

SARS-CoV-2 is a single-stranded-positive sense RNA (+ssRNA) virus which is larger than any other RNA viruses.[12] It is about 29,881 kb in length and encodes about 9860 amino acids.[13] The Covid-19 genome is enclosed in the nucleocapsid protein (N), and is surrounded by three protective structural proteins, such as membrane protein (M), envelop protein [E], and spike protein (S).[14] Addition, SARS-CoV-2 contains sixteen non-structural proteins (nsp1-nsp16), and several accessory proteins. Nsp1 mediates RNA processing and replication, whereas Nsp2 modulates the survival signaling pathway of host cells. Nsp12 contains the RNA-dependent RNA polymerase (RdRp), which plays a key role in coronavirus replication/transcription.[15] The Covid-19 spike proteins are decorated with polysaccharide molecules, which protect the spikes and enables SARS-CoV-2 to evade the host immune response.[16]

Spike glycoprotein

The entry of SARS-CoV-2 into human cells is facilitated by the spike glycoprotein (SP).[17, 18] The transmembrane SP project as homotrimers than gives Covid-19 its corona (crown) structure. The molecular size of the spike protein is about 180-200 kDa, and consists of 1273 amino acids. Structurally, it has an extracellular N-terminus, a transmembrane domain embedded in the membrane, and a short intracellular C-terminal.[19] Functionally, it is comprised of the N-terminus, a shorter S1 subunit, and a longer S2 subunit.

The S1 subunit consists of the N-terminal (NT), and the receptor binding domain (RBD), and its main function is to bind the virus to the receptor on host cells. The S2 subunit contains fusion peptide (FP), heptad repeat 1 (HR1), central helix (CH), connector domain (CD), heptad repeat 2 (HR2), transmembrane domain (TMD), and cytoplasmic tail (CT).[20] The function of S2 subunit is to fuse the membrane of virus to the membrane of host cells. The HR1 and HR2 form the six-helical bundle (6-HB) which is very important for the binding of the virus membranes to the host cells.[17-21]

Before infection the spike protein is in its inactive state. During Covid-19 infection the S protein has to be cleavage at the S1/S2 protease cleavage site. In most coronaviruses, host proteases, including the subtilisin-like host cell convertase furin, and transmembrane protease/serine subfamily 2 (TMPRSS2) cleave the spike glycoprotein at the S1/S2 cleavage site.[22] Spike protein priming by TMPRSS2 is essential for the entry of SARS-CoV-2 into human cells.[23] and for replication and spread of Covid-19.[24, 25] After cleavage of the S protein the RBD in the S1 subunit undergoes a conformation change (from a ‘’closed’’ to an ‘’open’’) configuration that enables exposure of receptor binding motif (RBM) to host cell receptors.[26, 27] This is crucial for the fusion of Covid-19 to the host cells through the irreversible confrontational changes, and activation of the protein for fusion.[28] Furthermore, furin cleavage of the S protein plays an important role in SARS-CoV-2 attachment, replication, and pathogenesis of Covid-19.[28]

SARS-CoV-2 enters into host cells by recognizing angiotensin-converting enzyme 2 (ACE2) on the host cell via its receptor binding domain.[22-30] Thereafter, its receptor-binding domain attaches to ACE2 on host cells. This causes a conformational change in S2 that leads in virus-host cell membrane fusion, and entry of the virus via clathrin-mediated endocytosis.[26] There are several other host receptors, such as amino peptidase N (APN), dipeptidyl peptidase 4 (DPP4), carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), and sugar recognize S1 domain of the spike protein which additionally facilitate virus entry into cells.[31]

The S1 subunit, epitopes on the receptor binding domain, and the RBM of SARS-CoV-2 are potential targets for the development of antiviral agents, monoclonal antibodies (mAbs), and vaccines for the treatment, and prophylaxis of SARS-CoV-2.[32] Monoclonal antibodies which specifically bind to RBM may prevent entry of SARS-CoV-2, and deter replication of Covid-19 in human cells. Thus preventing Covid-19-induced cytokine storm, which result in hyperinflammation.[33-35] diffuse alveolar damage (DAD), ARDS, respiratory failure, thromboembolism, myocardial injury,[36,37] and multi-organ failure.[38-39]

Pathophysiology

The immunopathological characteristics of SARS-CoV-2 is hyperinflammation due to host response to Covid-19, which results in overproduction of cytokines, chemokines, growth factors, proteases, and reactive oxygen species by monocytes, macrophages, and neutrophils (cytokine storm). The secreted pro-inflammatory mediators include cytokines, such as interleukin-1β (IL-1β), IL-2R, IL-6, IL-8, IL-10, IL-17, IL-18, tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and granulocyte-macrophage colony-stimulating factor.[40-44] Furthermore, several chemoattractant chemokines, including CCL2, CCL3, CCL5, CXCL8 (IL-8), CXCL9, and CXCL10; proteases; and growth factors are secreted by activated immune, and inflammatory cells during SARS-CoV-2 infection.[45-47] Table 1 shows pro-inflammatory cytokines, chemokines, and growth factors secreted during the cytokine storm, and SARS-CoV-2 infection.

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Table 1 Pro-inflammatory cytokines, chemokines, and growth factors secreted during the cytokine storm, and SARS-CoV-2 infection

Cytokines	Chemokines
Interleukin-1β (IL-1β)	CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10
IL-1Rα	Macrophage inflammatory protein-1 (MIP-1α/CCL3)
IL-2	Monocyte chemoattractant protein-1 (MCP-1/CCL2)
IL-4	Interferon gamma-induced protein 10 (IP-10/CXCL10)
IL-6	Growth factors
IL-8 (CXCL8)	Granulocyte colony-stimulating factor (G-CSF)
IL-9	Granulocyte-macrophage colony stimulating factor
IL-10	Platelet-activating factor (PAF)
IL-17	Fibroblast growth factor (FGF)
Tumor necrosis factor-α (TNF-α)	Hepatocyte growth factor (HGF)
Interferon-gamma (IFN-γ)	Vascular endothelial growth factor (VEGF)

Abbreviations: C-C: C-C motif chemokine ligand; CXCL: C-X-C, motif chemokine ligand; IL, Interleukin

The cytokines secreted during the cytokine storm, such as IL-6.[48] and GM-CSF.[49] are important targets for blockade in order to ameliorate the immunopathological damage caused by Covid-19, such as acute lung injury, respiratory failure, myocardial injury, and multi-organ damage. There are currently two IL-6 antagonists that have been granted emergency use authorization (EUA) by the US Food and drug Administration (FDA), including tocilizumab.[50] and sarilumab.[51] for the treatment of severe Covid-19 in hospitalized patients. Tocilizumab in combination with remdesivir and corticosteroids is used and effective in the treatment of severe SARS-CoV-2 in several countries.

GM-CSF plays an important role in lung parenchymal inflammation and acute ling injury, acting atop of the hierarchy of other pro-inflammatory cytokines in severe Covid-19 infection.[52, 53] Mavrilimumab is a GM-CSFRα human monoclonal antibody which inhibits the immunopathological effects of GM-CSF; and has shown good clinical outcomes in hospitalized patients for severe Covid-19 pneumonia with systemic hyperinflammation. Pupim et al.[54] have shown that mavrilimumab reduced the need for mechanical ventilation, and mortality by 65% at day 29 in critically ill non-mechanically ventilated patients with severe Covid-19 pneumonia. Interleukin antagonists, such as tocilizumab and mavrilimumab may be effective in early treatment of non-hospitalized patients with mild-to-moderate Covid-19.

RNA-dependent RNA polymerase

The replication of SARS-CoV-2 is controlled by a replication/transcription complex, and consists of several subunits. The complex is composed of viral non-structural proteins (nsp), and in the centre of the nsp12 is the RNA-dependent RNA polymerase (RdRp). RNA-dependent RNA polymerase catalyzes the synthesis of viral RNA, and is a critical component of coronavirus replication/transcription. RdRp is an important target for antiviral drug development, such as remdesivir (Veklury), and molnupiravir (Lagevir) which prevent replication of Covid-19, and retard spread of the virus. Remdesivir is the only antiviral agent which has been granted full approved by the US FDA for the treatment of severe hospitalized patients with SARS-CoV-2.[55]Whereas, molnupiravir has been granted an EUA for the treatment of severe Covid-19 in hospitalized patients.[56] Both biologics can be used to treat nonhospitalized patients with mild-to-moderate SARS-CoV-2. However, Lagevir is less effective than remdesivir, paxloid, and bebtelovimab, because it only reduces the risk of hospitalization and death by 30%. Therefore, it should only be used when the other three antivirals are not available.

Main protease

The main protease (M^{pro}), also referred to as 3CL protease of SARS-CoV-2 plays a key role in mediating the replication and transcription of viral genes. M^{pro} hydolyzes the polyprotein at eleven conserved sites to produce shorter, non-structural protein for viral replication. The main protease is an attractive target for the development of anti-proteases, and monoclonal antibodies, such as lopinavir-ritonavir (Kaletra), and nirmatrelvir-ritonavir (Paxlovid) have been repurposed for the treatment of patients with mild-to-moderate SARS-CoV-2. Paxlovid has been issued an EUA by the FDA for the treatment of non-hospitalized patients with mild-to-moderate Covid-19.[57]

Treatmement

Treatment of critically ill hypoxemic patients with Covid-19 is summerized in several national, and international treatment guidelines.[58, 59] The standard of care (SoC) include high-flow nasal oxygen (HFNO), corticosteroids, remdesivir, and interlekin-6 antagonists, such as tocilizumab, or a Janus kinase inhibitor, including baricitinib.[48-59]Critically ill patients with Covid-19 require admission to the intensive care units (ICU), invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO). However, ICU admission, and IMV or ECMO are associated with high hospital costs, prolonged multisystem disabilities, such as neurological impairment.[60] and excessive mortality rate.[61]

There are no standardized guidelines for the management of nonhospitalized patients with mild-to-moderate SARS-CoV-2. This has been problematic because of the continued mutations of Covid-19 variants, such as the Omicron variant of concern (VOC), which are resistant to the antivirals used to treat nonhospitalized patients. Furthermore, previously susceptible variants, such as Alpha, Beta, Gamma, and Delta have become resistant to some of the available antivirals and monoclonal antibodies. SARS-CoV-2 mutations are able to evade and elude host immune response, and resist novel targeted antivirals and monoclonal antibodies (mAbs).

Treatment of SARS-CoV-2 early before it progresses to severe disease with acute respiratory distress syndrome, respiratory failure, and multi-organ failure is highly recommended by the current guidelines in the management of Covid-19.[55-56] Spike protein inhibitors are the most suitable biotherapeutics for the treatment of mild-to-moderate SARS-CoV-2 before progression to severe fatal disease. Currently, there are four anti-spike monoclonal antibody therapies which have been granted an EUA by the FDA for the treatment of mild-to-moderate Covid-19 in adults and pediatric patients (12 years of age and older weighing at least 40 Kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe Covid-19, including hospitalization or death. They include: bamlanivimab-etesevimab.[62] casirivimab plus imdevimab.[63] sotrovimab.[64] and bebtelovimab.[65]

Bamlanivimab-etesevimab, and casarivimab-emdevimab are recombinant human mAbs that bind to different, but overlapping.[29-66] and nonoverlapping epitopes in the spike protein RBD of SARS-CoV-2,[67] respectively. Bamlanivimab-etesevimab.[60-70]and casirivimab plus imdevimab.[71-73] have shown clinical benefits in nonhospitalized patients with early mild-to-moderate Covid-19. Early treatment with the spike protein entry inhibitors has been associated with a relative risk reduction of hospitalization or death of about 70-80% in nonhospitalized patients with mild-to-moderate Covid-19.[69-74] Ronapreve, a combination of casirivimab and imdevimab has been shown to reduce the risk of hospital admission or death by 70% in high risk outpatients.[73] Similarly, bamlanivimab prophylaxis prevented hospital admission or death in 72-80% of residents and staff of skilled nursing and assisted living facilities exposed to Covid-19.[75] These results support the beneficial effects of early treatment with spike protein entry inhibitors in preventing progression of Covid-19 to respiratory failure, which may mandate the use of HFNO, and IMV or ECMO. Early treatment with spike entry inhibitors may prevent the necessity for IMV, and death from any cause due to Covid-19. Notwithstanding, IMV and ECMO are associated with high mortality rates in hospitalized patients in the intensive care units.

However, treatment with spike entry inhibitors in critically ill hospitalized patients requiring HFNO or IMV confers no benefit in terms of progression to severe disease, respiratory failure, MOF or death. Treatment with spike entry inhibitors is more successful in early Covid-19, and in patients without endogenous anti-SARS-CoV-2 antibodies, in contrast to patients with progressive Covid-19 with endogenous antibodies.[76] They are preferably administered within 5 days for antivirals, and 10 days for mAbs of onset of symptoms.

Bamlanivimab-etesevimab, and casarivimab-imdevimab are still effective against Alpha

(B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) variants, but have reduced efficacy against the Omicron (B.1.1.529), and BA.2 subvariants of concern. Henceforth, these entry inhibitors should not be used in countries where these Omicron sublineages are prevalent, including some States in the USA.[77]

Sotrovimab (Xevudy) is a fully human neutralizing IgG monoclonal antibody which was derived from convalescent plasma from a patient who survived SARS-CoV. It has a high affinity for binding to a highly conserved epitope of SARS-CoV-1 and SARS-CoV-2 spike glycoprotein outside the angiotensin-converting enzyme 2 (ACE2) receptor-binding motif.[78, 79] It has been modified using Xencor, Inc.'s Xtend™ technology, and its molecular structure has two amino acids in its fragment crystallisable (Fc) domain which increases its penetration in lung parenchyma, and airway tissue, and increases its median elimination half-life to approximately 49 days.[80, 81] Binding to a conserved SARS-CoV-2 spike protein epitope makes it more difficult for mutations to occur, and resistance to develop with sotrovimab. It has potential to block both SARS-CoV-1, and SARS-CoV-2 entry into host cells, and inhibit SARS-CoV-2 replication.[82]

Sotrovimab has been shown to maintain activity against Covid-19 variants of concern (VOC), such as Alpha B.1.7 (UK), Beta B.1.351 (South Africa), B.1.427/B.1.429 (Califonia), B.1.526 (New York, Gamma P.1 (Brazil), Delta Plus (AY.1 and AY.2), and Omicron sublineages, including Omicron B.1.1.529 (several countries).[82] However, sotrovimab is less effective against Delta B. 1.617.2 (India) due to the development of resistant mutations in the spike protein at positions 337 and 340.[83]

However, sotrovimab has been demonstrated to be an effective early treatment for patients with mild-to-moderate Covid-19. It has been shown to prevent hospitalization and progression of SARS-CoV-2 to acute hypoxemic respiratory failure, multiorgan failure, and death.[84-86]

In the COMET-ICE clinical trial, out of 291 patients who received sotrovimab 500 mg infusion, only 3 patients (1%) developed severe SARS-CoV-2 requiring hospitalization or who died. Conversely, in 292 patients who received placebo, 21 patients (7%) developed severe Covid-19 requiring hospitalization. Out of these patients, 5 patients were admitted to the intensive care unit (ICU), and one patient died on the 29th day after receiving placebo. No patients died in the sotrovimab treated group. Treatment with sotrovimab resulted in 85% (P = 0.002) relative risk reduction in hospitalization for more than 24 hours or death compared to placebo. Serious side-effects were less common with sotrovimab infusion compared to placebo, 2% and 6% of the patients, respectively. The common adverse events reported with sotrovimab were rash (2%), diarrhoea (1%), headache (1%), pyrexia, chills, dizziness, dyspnoea, pruritus, and light-headedness. All the adverse events were Grade 1 (mild) or Grade 2 (moderate.[87, 88]

In the second COMET-ICE randomized multi-centre clinical trial of 1057 non-hospitalized patients with mild-to-moderate SARS-CoV-2, hospitalization lasting more than 24 hours or death were significantly reduced with sotrovimab treatment (6/528 [1%]) compared to placebo (30/529 [6%]; P < 0.001).[89] Overall, sotrovimab showed a 79% significant reduction in the relative risk of hospitalization for more than 24 hours or death due to any cause by day 29 compared to placebo.[89]

All of the secondary outcomes, such as emergency department visits, hospitalization, progression to severe respiratory failure, or death were significantly reduced with sotrovimab compared to placebo. Adverse events were less common and similar between sotrovimab and placebo, 22% versus 23% of the patients, respectively. The common adverse effect with sotrovimab was diarrhoea (2%), and with placebo SARS-CoV-2 was pneumonia (4%).[89]

Sotrovimab is administered as an infusion of 500 mg/8 ml over 30 minutes. It is safe and well tolerated by patients, but patient must be observed during and after the infusion for any adverse events or anaphylaxis.[90]

Sotrovimab has been granted an Emergency Use Authorization (EUA) by the FDA for the treatment of mild-to-moderate SARS-CoV-2 in adults and paediatric patients 12 years of age and older weighing 40 kg and more with positive direct Covid-19 viral testing, and who are at high risk for progression to severe Covid-19, including hospitalization or death.[90]

Pre-clinical data has shown that sotrovimab has retained vitro and in vivo activity against most currently tested variants of concern and interest of the SARS-CoV-2 virus as defined by WHO, such as Delta (B.1.617), Delta Plus (AY.1 or AY.2), Mu (B.1.621).[82] and Omicron (B.1.1.529, BA.1, BA.1.1).[91, 92] However, it has decreased in vitro activity against Omicron BA.2.[93] Currently, the BA.2 sublineage infection is spreading like wild fire in the USA and has a prevalence of 50-70%. At the moment, the treatment guidelines from the National Institutes of Health and the FDA advise not to use sotrovimab for the treatment of patients with mild-to-severe SARS-CoV-2 in any state in the USA.[94] However, sotrovimab is still been used in other countries where the prevalence of Omicron BA-2 is less common; but there is still a possibility that Omicron BA.2 might develop resistance to sotrovimab in these countries. Recently, Destros et al.[95] have reported that Omicron BA.1 sublineage has developed mutations in the spike protein at positions 340 and 337; hence, sotrovimab might not be very effective against Omicron BA.1 in future.

Bebtelovimab (BEB) is a fully human IgG1 monoclonal antibody which targets the RBD of SARS-CoV-2 spike protein.[96] The mAb binds to an epitope that is highly conserved in most of the Covid-19 subvariants, which is different from the binding epitope of bamlanivimab (BAM) and etesevimab (ETE).[96] It binds to a rarely mutated epitope of SARS-CoV-2 spike protein making viral evasion difficult, and resistance rarely to develop. Bebtelovimab was derived from a convalescent blood sample from a patient with Covid-19. It has in vitro high potency and broad neutralizing activity to all the known Covid-19 variants of concern, such as Alpha, Delta, and Omicron subvariants including BA.2, BA.2.12.1, BA.4, BA.5, and BA.2.75.[96,97] BEB is the only authorized biologic capable of neutralizing all these subvariants of Omicron in addition to all the documented variants of concern, and psedoviruses carrying various single amino acid mutations.

Bebtelovimab has been demonstrated to significantly reduce the duration of symptoms in patients with mild-to-moderate SARS-CoV-2, and to significantly reduce the viral load of most of the Covid-19 VOC. It has been reported to reduce the risk of hospitalization by about 55.2%.[96]

In the BLAZE-4 clinical trial which enrolled 714 patients with mild-to-moderate SARS-CoV-2, bebtelovimab significantly reduced sustained symptoms by a median of 2 days compared to placebo (P = 0.002).[97] Bamlanivimab plus etesevimab only reduced symptoms by a median of 1 day compared to placebo (P = 0.289). BEB resolved symptoms in 6 days, BAM plus ETE resolved symptoms in 7 days, and placebo reduced symptoms in 8 days. However, the incidence of SARS-CoV-2-related hospitalization or death from any cause by day 29 were similar for all the study groups. Notably, treatment with both BEB, and BAM plus ETE was associated with significant reduction in the viral loads. All the biologics in the clinical trial were safe.[97] This study shows that monotherapy with bebtelovimab is comparable to that of bamlanivimab plus etesevimab. However, BEB has the advantage of neutralizing all the Covid-19 variants of concern, whereas, BAM and ETE are ineffective against most VOC, including BA.1, BA.2, and BA.1.529.

Bebtelovimab was granted an emergency use authorization by the US FDA for the treatment of mild-to-moderate COVID-19 in certain individuals 12 years of age and older, weighing 40 kg and more, with positive SARS-CoV-2 test, and who are at high risk for progression to severe COVID-19, including hospitalization or death.[98] Because of the risk of mutations in the Omicron variants, BEB can only be used as an alternative treatment option when the approved mAbs by the FDA are not accessible or when clinically appropriate.[99]

Other antivirals recommended for the treatment of outpatients include remdesivir.[100, 101] nirmatrelvir-ritonavir.[102] and molnupiravir.[103,104] which have remained active against SARS-CoV-2 Omicron, and other variants of concern. Table 2 shows the relative risk reductions in hospital admission or death in non-hospitalized patients with Covid-18 treated with SPIs.

Table 2 Relative risk reductions in hospitalization or death in nonhospitalized patients with mild-to-moderate Covid-19 treated with spike protein inhibitors

Monoclonal antibody	Target	Reduction in hospitalization
Bamlanivimab plus etesevimab	Spike protein	80%
Casirivimab plus imdevimab	Spike protein	70%
Sotrovimab (Xevudy)	Spike protein	85%
Bebtelovimab	Spike protein	55.20%
Remdesivir (Veklury)	RdRp	87%
Molnupiravir (Lagevrio)	RdRp	30%
Nirmatrelvir-ritonavir (Paxlovid)	Main protease	89.10%
Tixagevimab plus cilgavimab	Spike protein	PreP

Abbreviations: RdRp, RNA-dependent RNA polymerase; Evusheld (tixagevimab plus cilgavimab) is recommended for pre-exposure prophylaxis (PreP)

Spike protein inhibitors, such as tixagevimab plus cilgavimab (Evusheld) have been granted an EUA by the FDA for pre-exposure prophylaxis of Covid-19.[105, 106] Evusheld has been granted an EUA by the FDA for pre-exposure prophylaxis in individuals who have not been fully vaccinated against Covid-19 or are not expected to mount an adequate immune response to complete vaccination, and have been exposed to someone infected with SARS-CoV-2 or who are at high risk of exposure in an institutional setting, including nursing homes, and correction services. Tixagevimab co-packed with cilgavimab can also be used for pre-exposure prophylaxis in the elderly, obese, patients with chronic liver disease, chronic kidney disease, diabetes, solid tumours, haematological malignancies, and in patients on immunosuppressive therapy (see Fact Sheets for Healthcare Providers). Studies from Oxford and Washington Universities have shown that Evusheld retains neutralizing activity against Omicron subvariants.[107] However, pre-exposure prophylaxis should not be a substitute for observing National COVID-19 Guidelines, or vaccination, including booster mRNA Covid-19 vaccine.

Conclusion

Early treatment of Covid-19 is highly recommended in patients with mild-to moderate SARS-CoV-2 before they spread the infection to others, or progress to severe hypoxemic respiratory failure, requiring HFNO, IMV or ECMO. Spike protein entry inhibitors, such as bamlanivimab-etesevimab, casirivimab plus imdevimab, sotrovimab, and bebtelovimab have been shown to reduce the risk of progression of Covid-19, hospitalization, and death in nonhospitalized patients with SARS-CoV-2. However, bamlanivimab-etesevimab, and casirivimab plus imdevimab are not active against the latest Omicron subvariants. Sotrovimab and bebtelovimab are highly effective against most of the Covid-19 variants and the Omicron BA.1. However, sotrovimab has lost potency against Omicron BA.2 in most countries, including the USA. Therefore, only bebtelovimab is currently recommended for the treatment of nonhospitalized patients with mild-to-moderate SARS-CoV-2 in the USA and other countries. Other recommended antiviral and mAbs for the treatment of mild-to-moderate SARS-CoV-2 include remdesivir, ritonavir-boosted nirmatrelvir, and molnupiravir.

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References

1. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for the virus origins and receptor binding. *Lancet (London England).* 2020;395:565–574.
2. Wu Z, McGoogan JM. Characteristics of important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72, 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239–1242.
3. Gandhi RT, Malani PN, Del Rio C. COVID-19 therapies for nonhospitalized patients. *JAMA.* 2022;327(7):617–618.
4. Hu B, Guo H, Zhou P, et al. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol.* 2020;19:141–154.
5. Wang MY, Zhao R, Gao LJ, et al. SARS-CoV-2: structure, biology, and structure-based therapeutics development. *Front Cell Infect Microbiol.* 2020;10:587269.
6. Zhu FC, Li YH, Guan XH, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. *Lancet (London England).* 2020;395(10240):1845–1854.
7. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review in medical records. *Lancet (London England).* 2020;395(10226):809–815.
8. Tchesnokova V, Kulasekara H, Larson L, et al. Acquisition of the L452R mutation in the ACE2-binding interface of spike protein triggers recent massive expansion of SARS-CoV-2 variants. *J Clin Microbiol.* 2021;59(11):e0092121.
9. Larkin HD. Evolving omicron subvariants are more resistant to antibiotic therapy. *JAMA.* 2022;328(6):518.
10. Cao Y, Yisimayi A, Jian F, et al. BA-2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection. Nature. 2022;608(7923):593–602.
11. FDA updates sotrovimab emergency use authorization. News release. *US Food and Drug Administration. Accessed 5,2022.*
12. Liu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* 2020;395(10224):565–574.
13. Chen L, Liu W, Zhang Q, et al. RNA based mNGS approach identifies a novel human coronavirus from two individual pneumonia cases in 2019 Wuhan outbreak. *Emerg Microbes Infect.* 2020;9(1):313–319.
14. Huang Y, Yang C, Xu XF, et al. Structure and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. *Acta Pharmacologica Sinica.* 2020;41:1141–1149.
15. Naqvi AAT, Fatima K, Mohammad T, et al. Insights into SARS-CoV-2 genome, structure, evolution, pathogenesis and therapies: Structural genomics approach. *Biochim Biophys Acta Mol Basis Dis.* 2020;1866(10):165878.
16. Watababe Y, Ellen JD, Wrapp D, et al. Site-specific glycan analysis of the SARS-CoV-2 spike. Science 2020;369:330-333.
17. Li F, Li W, Farzan M, et al. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Sci.* 2005;309(5742):1864–1868.
18. Li F. Structure, function, and evolution of coronavirus spike proteins. *Annu Rev Virol.* 2016;3(1):237–261
19. Bosch BJ, van der Zee R, de Haan CA, et al. The coronavirus spike protein is a class 1 virus fusion protein: structure and functional characterization of the fusion core complex. *J Virol.* 2003;77(16):8801–8811.
20. Wang MY, Zhao R, Gao LJ, et al. SARS-CoV-2 structure, biology, and structured-based therapeutics development. *Front Cell Infect Microbiol.* 2020;10:587269.
21. Liu S, Xiao G, Chen Y, et al. Interaction between heptad repeat 1 and 2 regions in spike protein of SARS-associated coronavirus: implications for fusogenic mechanism and identification of fusion inhibitors. *Lancet (London England).* 2004;363(9413):938–947.
22. Hoffmann M, Kleine Weber H, Schroeder S, et al. SARS-CoV-2 entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181(2):271–280.
23. Hoffmann M, Kleine Weber H, Krüger N, et al. The novel coronavirus 2019 (COVID-19) uses SARS-1 coronavirus receptor and cellular protease TMPRSS2 for entry into target cells. *bioRxiv.* 2020.
24. Glowacka I, Bertram S, Muller MA, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome spike protein for membrane fusion and reduces viral control by humoral immune response. *J Virol.* 2011;85(9):4122–4134.
25. Iwata Yoshikawa N, Okamura T, Shimizu Y, et al. TMPRSS2 contributes to viral spread and immunopathology in the airways of murine models after coronavirus infection. *J Virol.* 2019;93(6):e01815–e01818.
26. Walls AC, Park YJ, Tortorici MA, et al. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell.* 2020;181(2):281–292.
27. Shang J, Ye G, Shi K, et al. Structural basis of receptor recognition by SARS-CoV-2. *Nature.* 2020;581(7807):221–224.
28. Zhou Y, Hou Y, Shen J, et al. Network-based drug repurposed for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discovery.* 2020;6:14.
29. Johnson BA, Xie X, Kalveran B, et al. Furin cleavage site is key to SARS-CoV-2 pathogenesis. *Preprint Server Biol.* 2020.
30. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature.* 2003;426(6965):450–454.
31. Hamming I, Timens W, Bulthuis MLC, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol.* 2004;203(2):631–637.
32. Jiang S, Hillyer C, Du L. Neutralizing antibodies against SARS-CoV-2 and other human coronaviruses. *Trends Immunol.* 2020; 41(5):355–359.
33. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat Microbiol.* 2020;5(4):562–569.
34. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020; 395(10229):1033–1034.
35. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497–506.
36. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'cytokine storm' in COVID-19. *J Infect.* 2020;80(6):607–613
37. Knight DS, Kotecha T, Razvi Y,et al. COVID-19: Myocardial injury in survivors. *Circulation.* 2020;142(11):1120–1122.

38. Hartmann C, dos Santos Miggiolaro AFR, da Silva Motta, et al. The pathogenesis of COVID-19 myocardial injury: an immunohistochemical study of postmortem biopsies. *Front Immunol*. 2021; 12:748417.

39. Tian S, Xiong Y, Liu H, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through post-mortem core biopsies. *Mod Pathol.* 2020;33:1007–1014.

40. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med.* 2020;8(4):420–422.

41. Del Valle DM, Kim-Schulze S, Huang HH, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med.* 2020;26:1636–1643.

42. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microbe.* 2020;27(6):992–1000.

43. Yang L, Liu S, Liu J, et al. COVID-19: Immunopathogenesis and Immunotherapeutics. *Signal Transduct Target Ther.* 2020;5:128.

44. Zhou Y, Fu B, Zheng X, et al. Pathogen T-cell inflammatory storm in severe COVID-19 patients. *Natl Sci Rev.* 2020;7(6):993–1002.

45. Kunnamakkara AB, Rana V, Parama D, et al. COVID-19, cytokines, inflammation, and spices: How are they related. *Life Sci.* 2021;284:119201.

46. Costela Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, et al. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. *Cytokine Growth Factor Rev.* 2020;54:62–75.

47. Khalil B, Elemam NM, Maghazachi ZA. Chemokines and chemoreceptors during COVID-19 infection. *Comput Struct Biotechnol J.* 202;19:976–988.

48. Ren Juan H, Wei Chieh Y, Guan Ru P, et al. The role of cytokines and chemokines in severe acute respiratory syndrome corona virus 2 infections. *Front Immunol.* 2022;13:832394.

49. Syabbalo N. The role of interleukin-6 and Janus kinases in the pathogenesis and treatment of SARS-CoV-2. *MARS Pulmonology.* 2022;9(1):17–32.

50. Favalli EG, Caporali R. GM-CSF in the treatment of COVID-19: a new conductor in the pathogenesis of cytokine storm? *Lancet Rheumatol.* 2020;2(8):e448–e449.

51. RECOVERY collaborative group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet.* 2021;397(10285):1637–1645.

52. CORIMUNO-19 collaborative group. Sarilumab in adults hospitalized with moderate-to-severe COVID-19 pneumonia (CORIMUNO-SARI-1): An open-label randomized controlled trial. *Lancet Rheumatol.* 2022;4(1):e24–e32.

53. Mehta P, Porter JC, Manson JJ, et al. Therapeutic blockade of granulocyte macrophage colony-stimulating factor in COVID-19-associated hyperinflammation: challenges and opportunities. *Lancet Respir Med* 2020;8(8):822–830.

54. Thwaites RS, Sanchez SUA, Siggins MK, et al. Inflammatory profiles across the spectrum of disease reveal a distinct role of GM-CSF in severe COVID-19. *Sci Immunol.* 2021;6(57):eabg9873.

55. Pupim L, Wang TS, Hudock K, et al. Mavrilumumab improves outcomes in phase 2 trial in non-mechanically-ventilated patients with severe COVID-19 pneumonia and systemic hyperinflammation. *BMJ Rheumatic Dis.* 2021.

56. CDER Statement: FDA's Veklury (remdesivir) approval for the treatment of COVID-19 – The Science of Safety and Effectiveness.2020.

57. Fact Sheet for Patients And Caregivers Emergency Use Authorization (EUA) Of LAGEVRIO™ (molnupiravir) capsules For Coronavirus Disease 2019; (COVID-19)

58. FDA. Fact sheet for healthcare providers: Emergency Use Authorization for *Paxloid*. 2022.

59. National Institutes of Health (NIH). COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Updated, 2021.

60. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America (IDSA) guidelines on the treatment and management of patients with COVID-19. *Clin Infect Dis*. 2020;ciaa478.

61. Ahmed JO, Ahmad SA, Hassan MN, et al. Post COVID-19 neurological complications; a meta-analysis. *Ann Med Surg (Lond).* 2022;76:103440.

62. Grasselli G, Zangrillo A, Zanella A, et al. COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of Lombardy region, Italy. *JAMA.* 2020;323(16):1574–1581.

63. Food and Drug Administration. Fact sheets for healthcare providers: emergency use authorization (EUA) of bamlanivimab and etesevimab. 2021.

64. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of REGEN-COV (casarivimab and imdevimab) 2921.

65. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of sotrovimab.2021.

66. FDA. Fact sheet for healthcare providers: Emergency Use Authorization for bebtelovimab.

67. Benton DJ, Wrobel AG, Xu P, et al. Receptor binding and priming of spike protein of SARS-CoV-2 for membrane fusion. *Nature.* 2020;588(7837):327–330.

68. Hansen J, Baum A, Pascal KE, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. *Science.* 2020;369(6506):1010–1014.

69. Gottlieb RL, Nirula A, Chen P, et al. Effects of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. *JAMA.* 2021;325:632–644.

70. ACTIV-3/TICO LY-CoV555 study Group. A neutralizing monoclonal antibody for hospitalized patients with COVID-19. *N Engl J Med.* 2021;384:905–914.

71. Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus etesevimab in mild or moderate Covid-19. *N Engl J Med.* 2021;385(15):1382–1392.

72. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-19. *N Engl J Med.* 2021;384(3):238–251.

73. Horby PW, Mafham M, Leon Peto, et al. RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *medRxiv.* 2021.

74. O'Brien MR, Forleo Neto E, Sarkar N, et al. Effect of subcutaneous casarivimab and imdevimab antibody combination vs placebo on the development of symptomatic COVID-19 in early asymptomatic SARS-CoV-2 infection. A randomized clinical trial, *JAMA*. 2022;1;327(5):432–441.

75. Mahase E. Covid-19: UK approves first monoclonal antibody treatment. *BMJ.* 2021;374:n2083.

76. Cohen MS, Nirula A, Mulligan MJ, et al. Effect of bamlanivimab vs placebo on incidence of COVID-19 among residents and staff of skilled nursing and assisted living facilities: a randomized clinical trial. *JAMA.* 2021;326(1):46–55.

77. Lundgren JD, Grund B, Christina E.B, et al. ACTIV-3/TICO Bamlanivimab Study Group. Clinical and virological response to a neutralizing monoclonal antibody for hospitalized patients with COVID-19. *medRxiv.* 2021.

Citation: Syabbalo N. The role of spike protein entry inhibitors in the treatment of mild-to-moderate covid-19 in nonhospitalized patients. *J Lung Pulm Respir Res.* 2022;9(2):52–59. DOI: 10.15406/jlprr.2022.09.00280

78. Centers for Disease Control and Prevention. COVID data tracker: variant proportions. 2021.

79. Starr TN, Greaney AJ, Dingens AS, et al. Complete map of SARS-CoV-2 RBD mutations that escape the monoclonal antibody LY-CoV555 and its cocktail with LY-CoV016. *Cell Rep Med.* 2021;2(4):100255.

80. Liu H, Wei P, Zhang Q, et al. 501Y.V2 and 501.V3 variants of SARS-CoV-2 lose binding to bamlanivimab in vitro. *MAbs*. 2021; 13(1):1919285.

81. Pinto D, Park YJ, Beltramello M, et al. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. *Nature.* 2020;583(7815):290–295.

82. Gaudinski MR, Coates EE, Houser KV, et al. VRC 606 study Team. Safety and pharmacokinetics of the Fc-modified HIV-1 human monoclonal antibody VRC01LS: a phase 1 open-label clinical trial in healthy adults. *PLoS Med.* 2018;15(1):1002493.

83. Cathcart AL, Havenar-Daughton C, Lempp FA, et al. The dual function monoclonal antibodies VIR-7831 and VIR-7832 demonstrate potent in vitro and in vivo activity against SARS-CoV-2. *bioRXiv.* 2021.

84. Rockett R, Basile K, Maddocks S, et al. Resistance mutations in SARS-CoV-2 delta variant after sotrovimab use. *N Engl J Med.* 2022;386:1477–1479.

85. GlaxoSmithKline. Vir Biotechnology and GSK announce VIR-7831 reduces hospitalisation and risk of death in early treatment of adults with COVID-19.

86. Brii Biosciences. Brii Bioscience announces positive data from phase 3 ACTIV-2 trial evaluating BRII-196 and BRII-198 in non-hospitalized COVID-19 patients. 2021.

87. Tuccori M, Ferraro S, Convertino I, et al. Anti-SARS-CoV-2 neutralizing monoclonal antibodies:clinical pipeline. *MAbs.* 2020; 121854149.

88. Gupta A, Gonzalez-Rojas Y, Juarez E, et al.for the COMET-ICE Investigators. Early Covid-19 treatment with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med.* 2021.

89. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. for the COMET-ICE Investigators. Early Covid-19 treatment with SARS-CoV-2 neutralizing antibody sotrovimab. *medRxiv.* 2021.

90. Gupta A, Gonzalez Rojas Y, Juarez E, et al. for the COMET-ICE Investigators. Effect of sotrovimab on hospitalization or death among high-risk patients with mild to moderate COVID-19 A randomized clinical trial. *JAMA.* 2022;327(13):1236–1246.

91. US Food and Drug Administration Fact sheet for healthcare providers emergency use authorization (EUA) of sotrovimab.

92. Planas D, Saunders N, Maes P, et al. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. *Nature.* 2021.

93. Cameroni E, Saliba C, Bowen JE, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. *bioRxiv.* 2021.

94. Bruel T, Hadjadj J, Maes P, et al. Serum neutralization of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies. *Nat Med.* 2022.

95. FDA updates sotrovimab emergency use authorization. News release. *US Food and Drug.* 2022.

96. 94. Westendorf K, Wang L, Zentelis S, et al. LY-Co1404 (bebtelovimab) potently neutralizes SARS-CoV-2 variants. *bioRxiv.* 2022.

97. Destras G, Bal A, Simon B, Lina B, Josset L. Sotrovimab drives SARS-CoV-2 omicron variant evolution in immunocompromized patients. *Lancet Microbe*. 2022.

98. US Food and Drug Administration. Coronavirus (covid-19) update: FDA authorizes new monoclonal antibody for treatment of covid-19 that retains activity against omicron variant, 2022.

99. Dunleavy K. FDA signs off on Lilly's new antibody drug, bebtelovimab, which is effective against the omicron variant. *Fierce Pharma*. 2022;05:42.

100. Dougan M, Azizad M, Chen P, et al. Bebtelovimab, alone or together with bamlanivimab and etesevimab as a broadly neutralizing monoclonal antibody treatment for mild to moderate ambulatory COVID-19. *medRxiv.* 2022.

101. FDA. Emergency Use Authorization (EUA) for the Treatment of COVID-19. Fact Sheets – Healthcare Providers (English).

102. US National Institutes of Health.Therapeuptic management of nonhospitalized adults with covid-19, 2022.

103. Vangeel L, De Jonghe S, Peit Maes P, et al. Remdesivir, molnupiravir and nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern. *bioRxiv.* 2022.

104. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. *N Engl J Med.* 2021.

105. Hammond J, Leister-Tebbe H, Gardner A, et al. for the EPIC-HR Investigators. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *N Engl J Med*. 2022.

106. Fischer V, Eron JJ Jr, Holman W, et al. Molnupiravir, an oral antiviral treatment for COVID-19. *medRxiv*. 2021.

107. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. for the MOVe-OUT Study Group. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. *N Engl J Med.* 2021.

108. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Evusheld (tixagevimab co-packed with cilgavimab), 2022.

109. US Food and Drug Administration. Coronavirus (covid-19) update: FDA authorizes new monoclonal antibody for treatment of covid-19 that retains activity against omicron variant, 2022.

110. EVUSHELD long-acting antibody combination retains neutralizing activity against Omicron variants in studies from Oxford and Washington Universities. *AstraZeneca.* 2021.

Citation: Syabbalo N. The role of spike protein entry inhibitors in the treatment of mild-to-moderate covid-19 in nonhospitalized patients. *J Lung Pulm Respir Res.* 2022;9(2):52–59. DOI: 10.15406/jlprr.2022.09.00280