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MINIREVIEWS

Monoclonal antibody for COVID-19: Unveiling the recipe of a new cocktail

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has had a tremendous adverse impact on the global health system, public sector, and social aspects. It is unarguably the worst pandemic of the century. However, COVID-19 management is a mystery in front of us, and an authentic treatment is urgently needed. Various repurposed drugs, like ivermectin, remdesivir, tocilizumab, baricitinib, *etc*., have been used to treat COVID-19, but none are promising. Antibody therapy and their combinations are emerging modalities for treating moderate COVID-19, and they have shown the potential to reduce hospitalisations. One antibody monotherapy, bamlanivimab, and two cocktails, casirivimab/imdevimab and bamlanivimab/esterivimab, have received authorization for emergency use by the United States Food and Drug Administration for the treatment of mild COVID-19 in high risk individuals. The European Emergency has made similar recommendations for use of the drug in COVID-19 patients without oxygen therapy. This brief review will focus on monoclonal antibodies and their combination cocktail therapy in managing COVID-19 infection.

Key Words: SARS-CoV-2; Mild COVID-19; Antibodies; Risk factors

Core Tip: The coronavirus disease 2019 (COVID-19) pandemic is a severe public health emergency that necessitated the rapid development of novel medicines and viral detection technologies. Monoclonal antibodies against the receptor-binding domain of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein have become an important target for the creation of therapeutic antibodies. The use of antibody cocktails is anticipated to be a key component of an efficient COVID-19 treatment plan because SARS-CoV-2 has a high mutation rate, particularly when subjected to the selection pressure of aggressively applied preventive vaccinations and neutralising antibodies.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has placed a high burden on healthcare systems globally[1]. The first case of COVID-19 was reported on January 30, 2020. As of July 20, 2021, India had the highest number of COVID-19 instances, with more than 30 million[2]. The second wave of COVID-19 was more severe than the first. There was a reported shortage of drugs, oxygen, hospital beds, and vaccines. Some patients with COVID-19 will develop acute disease and multiorgan complications, but there are currently no proven therapeutics to prevent or reduce COVID-19 related hospitalisations, complications, or mortality.

Various drugs are approved for patients hospitalised with severe COVID-19 infection, but only a few drugs for mild COVID-19 patients who are not sick enough to be hospitalised are available[3]. Monoclonal antibodies (mAbs) are a new treatment for mild COVID-19 outpatients with a high risk. Recently, cocktail therapy has been approved for mild to moderate COVID-19 patients. Immunity to viral infection is a multipronged response, comprising the innate response-which restricts viral replication and creates an antiviral state in the local tissue environment, the adaptive response- in which virus-specific CD4+ T cells, CD8+ T cells, and the antibodies produced by B cells to control and clear the infection and generate immune memory. COVID-19 appears to evade or delay the innate immune response. If adaptive immunity is delayed for too long (because of efficient viral evasion, diminished innate immunity in the patient, or both), then the inability to control infection puts patients at an increased risk for severe or even fatal COVID-19 disease[4].

Despite recent studies demonstrating immune responses to COVID-19 as far as up to 8 mo after symptom onset, much remains to be learned about post-infection immunity to COVID-19[5,6]. Immunity to seasonal human coronaviruses is usually of short duration, and reinfection has been documented in patients who have already been infected with COVID-19[7]. Moreover, some individuals might not benefit from vaccination, as the vaccine trials published to date have not shown 100% efficacy, and real-world experience has demonstrated breakthrough events[8,9]. Furthermore, large parts of the population are still not vaccinated primarily because of supply issues and in part because of vaccine hesitancy. Thus, there is a pressing need for alternative therapies for COVID-19 patients. This article reviewes the currently approved cocktail therapy(-ies) in the management of COVID-19 disease.

WHAT ARE MABS?

An antibody is a protein molecule naturally developed by the immune response to infection. Antibodies are an essential factor in immunity against most viral diseases. Monoclonal antibodies **(**mAbs) are a single isotype with a defined specificity targeting with high potency a particular antigen *via* the antigen-binding fragment. As such, mAbs against COVID-19 have been derived from plasma donated by patients who recovered from COVID-19[10]. Polyclonal antibodies are usually defined as a mixture of diverse antibodies with mixed affinities for their targets. However, in the world of COVID-19 therapeutics, the term "polyclonal antibodies" is more descriptive of convalescent plasma with several antibody components[11].

mAbs are designed in a laboratory and mimic the natural immune system in response to infection. They are created for a specific target of infectious particles. A mAb is produced by exposing white blood cells to a particular viral protein cloned to produce antibodies to treat several infections and cancers [12]. mAbs that bind to the spike (S) protein of the COVID-19 virus stop the virus from binding the angiotensin-converting enzyme II (ACE2) receptor of human cells and prevent its invasion and replication[13]. mAbs have been effective against new COVID-19 variants B.1.1.7.

Even though more than 75 mAbs have been licensed by the United States Food and Drug Administration (FDA), only three are used to treat or prevent infectious diseases like anthrax, respiratory syncytial virus, and *Clostridium difficile*, and two are used to treat Ebola virus diseases. mAbs are intended for patients recently diagnosed with COVID-19 who are not very sick and have risk factors for severe infection[14-16].

This article focuses on mAbs with neutralising activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which work by targeting the receptor binding domain (RBD) of the viral S protein, thereby preventing viral attachment to the ACE2 receptor and preventing a critical step in viral entry and infection. Bamlanivimab is a recombinant, neutralising human immunoglobulin G1 (IgG1) mAb effective against the S protein of COVID-19. Etesevimab is a recombinant, fully human monoclonal neutralising antibody that binds to the surface S protein receptor-binding domain with high affinity and blocks viral binding to the ACE2 receptor of the host cell surface. Imdevimab and Casirivimab are IgG1 that act against SARS-CoV-2 S protein. Thus, the antibody cocktail thwarts the attachment of the virus and its entry into the human cell.

MABS THERAPY: SCIENTIFIC EVIDENCE

Casirivimab (REGN10933) and imdevimab (REGN 10987) were developed by Regeneron F and Hoffmann-La Roche Ltd pharmaceuticals, respectively, and bamlanivimab and the cocktail of bamlanivimab and esterivimab were developed by Eli Lilly and AbCellera, respectively. The following studies or their scientific data reveal how these mAbs are helpful in treating COVID-19 (Table 1).

BLAZE-1

The BLAZE 1 trial was a phase 2/3 trial that enrolled 452 ambulatory COVID-19 patients and was given bamlanivimab as one of three doses [bamlanivimab (LYCoV555) -700 mg, 2800 mg, or 7000 mg in intravenous (IV) infusion] or placebo. The quantitative virologic endpoints and clinical outcomes were assessed[17]. The immediate result was the change in the viral load by day 11. For patients who received a 2800 mg (middle) antibody dose, viral load decreased by a factor of 3.4. The patients who received the 700 mg (lower) dose or the 7000 mg (higher) amount showed a more negligible difference from the placebo in the viral load change from baseline. In addition, bamlanivimab antibody therapy resulted in fewer hospitalisations and/or emergency room visits (1.9% in 2800 mg treatment group compared to 6.3% in the placebo group).

ACTIVE-3

The ACTIVE -3 trial enrolled 314 (163 drug group and 151 placebo group) hospitalised COVID-19 patients without end organ failure[18]. All the patients were also on supportive care as background therapy, including an antiviral drug and when indicated, supplemental oxygen and glucocorticoids. Bamlanivimab at a 7000 mg or placebo dose was administered as a single IV infusion over 1 h. The results revealed that mAbs when administered with remdesivir did not show efficacy among hospitalised COVID-19 patients without end organ failure.

BLAZE-2

This randomised phase 3 clinical trial enrolled 966 residents and staff at a United States nursing facility with at least one confirmed COVID-19 index case and who were negative at baseline for COVID-19 infection and serology. The incidence of COVID-19 disease among those treated with the antibody bamlanivimab *vs* placebo (8.5% *vs* 15.2% respectively) was lower[19]. Bamlanivimab monotherapy compared with a placebo reduced the risk of COVID-19 in residents and staff of nursing facilities.

COCKTAIL THERAPY

Bamlanivimab and etesevimab

The BLAZE-1 phase 3 trial showed that the cocktail of bamlanivimab and etesevimab was associated with a significant reduction in viral load compared to the placebo. In contrast, bamlanivimab monotherapy did not result in a substantial reduction. The cocktail was also shown to reduce the number of hospitalisations. The trial included 518 patients in the treatment arm who received a single infusion of bamlanivimab 2800 mg and etesevimab 2800 mg together, and 517 patients received a placebo[20]. The primary endpoint was COVID-19 related hospitalisations or death by any cause during the 29-d follow-up. Hospitalisation or death occurred in 36 (7%) patients who received a placebo compared to 11 (2%) patients treated with bamlanivimab and etesevimab together (a 70% reduction). Ten deaths (2%) deaths occurred in the placebo group. Thus, all-cause death was significantly lower in the bamlanivimab and etesevimab group compared to the placebo group. The United States FDA granted Emergency Use Authorisation (EUA) for the 700 mg dose of bamlanivimab for ambulatory

Table 1 Properties of different studies of antibodies therapy in coronavirus disease 2019

Ref.	Study type	Dose and duration	Primary outcome	Secondary outcomes	Primary result	Additional characteristics	Adverse effects
Chen *et al* [17], BLAZE-1	Randomised, double-blind, placebo-controlled, single-dose trial	Total 452 patients; 309 in the bamlanivimab (LY-CoV555) group and 143 in the placebo group. mAb at doses of 700 mg, 2800 mg, and 7000 mg and placebo administered within 3 d after positive SARS-CoV-2 results	The change from baseline to day 11 (4 d) in SARS-CoV-2 viral load	COVID-19 related inpatient hospitalisation, a visit to the emergency department, death, safety, symptom severity, and time points for viral clearance	The viral load at day 11 was lower in patients who received 2800 mg drug compared to the placebo group	High-risk subgroups (an age of ≥ 65 yr or a BMI of ≥ 35), the percentage of hospitalisation was 4.2% in the LY-CoV555 group and 14.6% in the placebo group	Serious adverse events occurred in none of the patient treatment groups, diarrhoea was reported in 3.2% of the patients
Weinreich *et al*[23], REGN-COV2	Double-blind, phase 1-3 trial, 275 (1:1:1) non-hospitalised patients with COVID-19	REGN-COV2 is a combination of casirivimab (REGN10933) and imdevimab (REGN10987). Among the 275 patients, 90 were assigned to receive high-dose (8.0 g), 92 to receive low-dose (2.4 g), and 93 to receive placebo	The time-weighted average change in viral load from baseline (day 1) through day 7	The percentage of patients with at least one COVID-19 related medically attended visit through day 29	REGN-COV2 enhanced clearance of virus, particularly in patients in whom an endogenous immune response had not yet been initiated	The median age was 44.0 yr, 49% were male, 13% identified as Black or African American, and 56% as Hispanic or Latino	In this interim analysis, both REGN-COV2 doses (2.4 g and 8.0 g) were associated with few and low-grade toxic effects (1%) in the combined REGN-COV2 dose groups
Gottlieb *et al*[20], BLAZE 1	Multipart, 49 United States centres including phase 2/3, randomised, double-blind, placebo-controlled, single-infusion study (BLAZE-1) ambulatory patients (n = 613) and had one or more mild to moderate symptom	Patients were randomised to receive a single infusion of bamlanivimab [700 mg (n = 101), 2800 mg (n = 107), or 7000 mg (n = 101)], the combination treatment (2800 mg of bamlanivimab and 2800 mg of etesevimab (n = 112), or placebo (n = 156)	Change in SARS-CoV-2 log viral load at day 11 (± 4 d)	A total of nine prespecified secondary outcome measures were evaluated. Three focused on viral load (time to viral clearance; the proportion of patients with viral support at days 7, 11, 15, and 22; time to symptom improvement; time to symptom resolution; and the balance of patients showing symptom improvement or resolution at days 7, 11, 15, and 22), and 1 focused on clinical outcomes (the proportion of patients with a COVID-19 related hospitalisation, emergency department visit, or death) at day 29	Among the 577 patients who were randomised and received an infusion, 533 (92.4%) completed the efficacy evaluation period (day 29). The change in log viral load from baseline at day 11 was –3.72 for 700 mg, –4.08 for 2800 mg, –3.49 for 7000 mg, –4.37 for combination treatment, and –3.80 for placebo	The mean age of patients was 44.7 ± 15.7 yr. A total of 315 patients (54.6%) were female, 245 patients (42.5%) identified as Hispanic, and 387 patients (67.1%) had at least one risk factor for severe COVID-19 (aged ≥ 55 yr, BMI ≥ 30, or ≥ 1 relevant comorbidity such as hypertension)	Immediate hypersensitivity reactions were reported in 9 patients (6 bamlanivimab, 2 combination treatment, and 1 placebo). No deaths occurred during the study treatment
BLAZE-2 [21]	Randomised, double-blind, single-dose, phase 3 placebo-controlled trial, 966 participants (300 residents and 666 staff) who tested negative for SARS-CoV-2 at baseline	Bamlanivimab 4200 mg or placebo only if a nursing home recorded at least one confirmed case of SARS-CoV-2 infection among residents or facility staff from a sample collected within the last 7 d	To find incidence of COVID-19, defined as the detection of SARS-CoV-2 by reverse transcriptase-PCR and mild or worse disease severity within 21 d of detection, within 8 wk of randomisation	To find incidence of moderate or worse COVID-19 severity and incidence of SARS-CoV-2 infection	Bamlanivimab significantly reduced the incidence of COVID-19 in the prevention population compared with placebo [8.5% *vs* 15.2%; odds ratio: 0.43 (95%CI: 0.28-0.68); P < 0.001]; absolute risk difference, −6.6 (95%CI: −10.7 to −2.6 percentage points)	Significantly reduced the incidence of moderate or worse COVID-19 compared with placebo (8.3% *vs* 14.1%)	The rate of participants with adverse events was 20.1% in the bamlanivimab group and 18.9% in the placebo group. The most common adverse events were urinary tract infection (2.0%) in bamlanivimab and (2.4%) placebo and hypertension (1.2%) in bamlanivimab and (1.7%) placebo
Lundgren *et al*[18],	Randomised, double-blind, placebo-	Hospitalised COVID-19 patients (n = 314) without	A sustained recovery, as assessed in a time-to-	Death from any cause	Hospitalised patients with COVID-19 who received mAb	The majority of patients had hypoxemia and tested the	Serious adverse events (19%) in the LY-CoV555 group and

ACTIVE-3	controlled trial	end organ failure, single infusion of the neutralising mAb antibody LY-CoV555 (at a dose of 7000 mg)	event analysis, through day 90 as well as two ordinal outcomes that were measured at day 5		did not have better clinical outcomes at day 5 than those who received placebo	effect of LY-CoV555 on a background of remdesivir and substantial glucocorticoid therapy	(14%) in the placebo
REGN-COV2067[24]	Phase (I-III) adaptive randomised placebo control double-blind	COVID-19 in infected non-hospitalised patients (n = 4567; REGN-COV2067)	1200 mg cocktail (n = 736), placebo (n = 748), and another group cocktail dose 2400 mg IV (n = 1355), placebo (n = 1341)	Clinically significant effect on risk of COVID-19 hospitalisation or all-cause death in high-risk non-hospitalised patients and confirm safety	Cocktail of casirivimab and imdevimab significantly reduced the risk of hospitalisation or death by 70% (1200 mg IV) and 71% (2400 mg IV) compared to placebo	Cocktail therapy reduced symptom duration from 14 d to 10 d (median numbers)	Not mentioned

BMI: Body mass index; COVID-19: Coronavirus disease 2019; IV: intravenous; mAb: Monoclonal antibody; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

COVID-19 patients at high risk[21,22].

The EUA advised the population on the benefits of monotherapy despite uncertainties[21,22]. The authorised dosage of 700 mg bamlanivimab and 1400 mg etesevimab administered together was based on analyses of available preclinical, clinical, and virologic data as well as pharmacokinetic and pharmacodynamic modelling, which supported that the authorised dosage was expected to have a similar clinical and virologic effect to 2800 mg bamlanivimab and 2800 mg etesevimab administered together.

Casirivimab and imdevimab

REGN-COV-2: The mAbs casirivimab and imdevimab bind to the non-overlapping portion of the RBD. A phase 1/2/3 trial (NCT04425629) is taking place across several countries. The phase 3 trial results have been reported. The trial enrolled 4576 patients with one risk factor for severe COVID-19, and an IV infusion of 1200 mg or 2400 mg caserivimab/imdevimab *vs* placebo was given. The trial reached its primary outcome and depicted that the casirivimab and imdevimab cocktail significantly reduced the risk of hospitalisation or death by 70% in the 1200 mg dose arm and 71% in the 2400 mg dose arm; both were significant compared with placebo[23]. In addition, benefits in the secondary outcomes were also found, including a 4-d reduction in the median duration of symptoms *vs* placebo.

Interim data from the first 275 patients (phase 1/2 portion) revealed that the cocktail showed virological efficacy resulting in an overall reduction in viral load of 0.25 log10 RNA copies/mL (95%CI: 0.60, 0.10) for the 2400 mg dose and a reduction of 0.56 log10 RNA copies/mL (95%CI: 0.91, 0.21) for an 8000 mg dose (combined dose reduction was 0.41 log10 RNA copies/mL, 95%CI: 0.71, 0.10) *vs* placebo at day 7.

No data on infectious virus titres or time to the cessation of viral shedding endpoints have been reported, similar to the situation with bamlanivimab or other mAb studies. An ongoing dose-ranging phase 2 companion trial in low-risk symptomatic or asymptomatic non-hospitalised patients with COVID-19 (NCT04666441) showed significant and comparable viral load reductions in casirivimab/imdevimab doses ranging from 300 mg to 2400 mg delivered *via* IV or subcutaneously (SC). The casirivimab/imdevimab cocktail has received EUA by the United States FDA for the treatment of ambulatory patients with mild to moderate COVID-19 and a high risk of hospitalisation, and the EUA

has similarly recommended casirivimab/imdevimab for use in COVID-19 patients who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 (Figure 1).

A trial showed that SC injection of the antibody cocktail casirivimab and imdevimab reduced the risk of symptomatic COVID-19 infection by 81% in household contact with an infected person without COVID-19 antibodies. The trial was conducted by the National Institute of Allergy and Infectious Disease. The individuals treated with the cocktail therapy with symptoms were relieved in 1 wk compared to 3 wk in placebo. The FDA has given EUA for the use of casirivimab and imdevimab antibody combination for the treatment of mild to moderate COVID-19 in adults and children over 12 years and weigh more than 40 kg who are at high risk for progressing to severe disease/hospitalisation. The trial showed that the cocktail antibodies casirivimab and imdevimab were more effective when given as early as possible[24]. The Indian drug regulatory body, the Central Drugs Standards Control Organisation, has recently approved the cocktail regimen for use in the country in the fight against COVID-19. The drug, marketed by Cipla Inc. in India, is currently in vogue for clinical use[25].

Another contemporary mAb has been evaluated and is primarily targeted against the COVID-19 S protein. Sotrovimab, a mAb, also blocks the attachment and viral entry into the host cell. A phase 1/2/3 double-blind placebo-controlled trial enrolled 583 non-hospitalised mild to moderate COVID-19 adult patients. Of these, 291 received sotrovimab, and the rest received a placebo within 5 d of symptoms. The primary endpoint was hospitalisation or death through day 29. The result showed 21 (7%) patients were hospitalised or died in the placebo arm compared to 3 (1%) patients in the sotrovimab group. An 85% reduction in hospitalisation or death in the treatment group was observed[26]. Sotrovimab showed activity against the current variants reported in the United Kingdom, South Africa, Brazil, California, New York, and India. The EUA recommends a 500-mg single IV dose of sotrovimab for non-hospitalised mild to moderate COVID-19 patients[27].

WHICH GROUPS ARE SUITABLE FOR MAB?

mAb therapies have shown promise for treating non-hospitalised patients with mild to moderate COVID-19. The EUA recommends that mAb treatment be given within 10 d of symptom onset or as early as 72 h of positive COVID-19 result. However, treatment should begin as early as possible to mitigate viral proliferation. In the REGN-COV2 study, the effect of REGN-COV2 on viral load was most pronounced among patients with a negative serum antibody test result at baseline. Furthermore, most trials administered mAb treatment within 3 d of a positive COVID-19 test result and a median of 3- 4 d after symptom onset. Altogether, these studies suggest that early mAb treatment is more efficacious than the later treatment for COVID-19 patients. Indeed, by the time a patient reaches the lung injury phase of infection, it is too late for mAb treatment to be effective, as suggested by the results from the ACTIV-3 study (Figure 2).

Route, dose, and cost of mAbs

A 600 mg of each or a combined 1200 mg of the caserivimab and imdevimab cocktail has been approved for administration. This can be given either IV or SC. The administration of a total dose of cocktail antibody takes around 30 min. The patient should be kept on observation for 1 h to check for any adverse effects. The price for a dose of 1200 mg cocktail (600 mg of caserivimab and 600 mg of imdevimab) is INR 59750 (700 USD approx). This drug should be stored at 2-8 ^{o}C.

Efficacy and safety

The clinical efficacy and safety profiles do not differ between mAb monotherapy and cocktails. Yet, monotherapy *vs* combination therapy is particularly relevant given the emergence of variant strains from the United Kingdom, South Africa, Brazil, California, New York, and India. The results from one study suggested that a mAb cocktail, particularly one combining antibodies that bind distinct and non-overlapping regions, can minimise mutational escape[28]. More importantly, viral mutations can reduce the effectiveness of mAb monotherapy. A recent preprint publication reported that bamlanivimab and casirivimab are effective against the South African variant. Several variants have been labelled by the Centers for Disease Control and Prevention as "variants of concern" because the mutations they carry increase transmission, increase disease severity, and reduce the efficacy of mAb therapy and vaccinations.

CONCLUSION

There is growing evidence that mAb treatment is effective, safe, and well-tolerated. Patients should know that mAb treatment is available to all patients at a high cost in India and that mAb treatment should be started within 72 h of a positive COVID-19 test result to affect the clinical course of COVID-19. Further studies on mAb efficacy and safety in different patient populations (*e.g.*, young children and

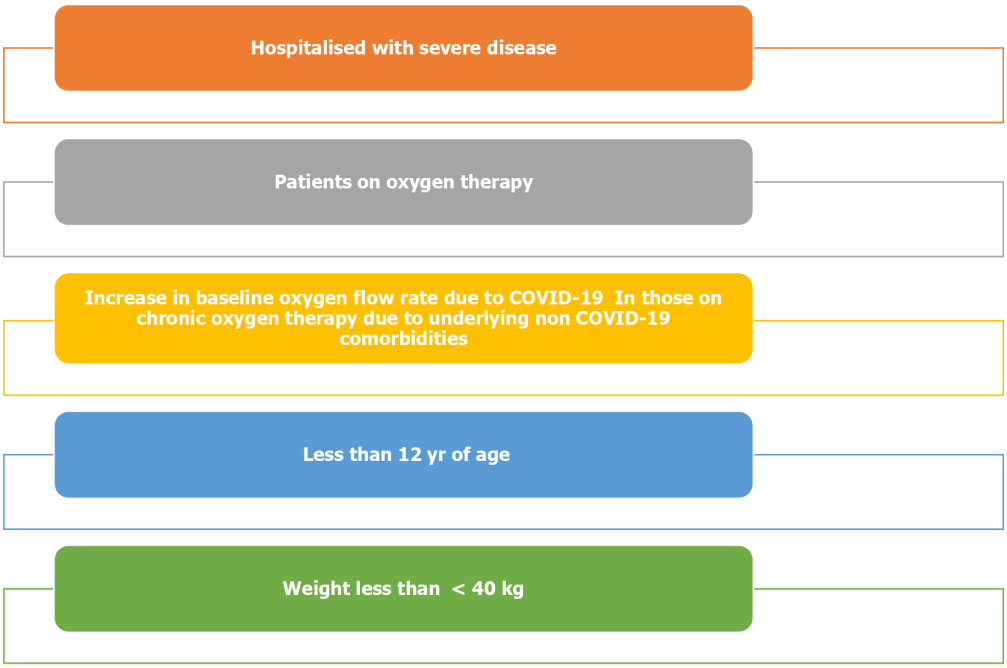

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Figure 1 Contraindications of monoclonal antibody therapy. COVID-19: Coronavirus disease 2019.

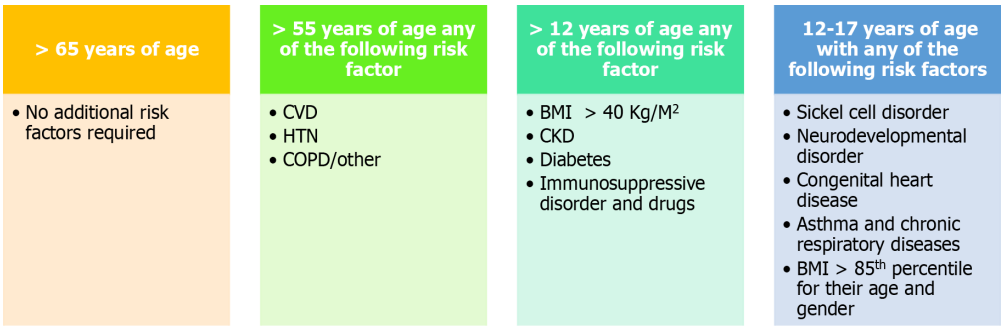

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Figure 2 High-risk groups indicated for treatment with monoclonal antibodies. CVD: Cardiovascular disease; HTN: Hypertension; COPD: Chronic obstructive pulmonary disease; BMI: Body mass index; CKD: Chronic kidney disease.

pregnant women) are needed.

FOOTNOTES

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CASE REPORT

Pulmonary arterial hypertension confirmed by right heart catheterization following COVID-19 pneumonia: A case report and review of literature

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Abstract

BACKGROUND

Pulmonary arterial hypertension (PAH) is a disease of the arterioles resulting in an increased resistance in pulmonary circulation with associated high pressures in the pulmonary arteries, causing irreversible remodeling of the pulmonary arterial walls. Coronavirus disease 2019 (COVID-19) has been associated with development of new onset PAH in the literature leading to symptoms of dyspnea, cough and fatigue that persist in spite of resolution of acute COVID-19 infection. However, the majority of these cases of COVID related PAH were diagnosed using echocardiographic data or *via* right heart catheterization in mechanically ventilated patients.

CASE SUMMARY

Our case is the first reported case of COVID related PAH diagnosed by right heart catheterization in a non-mechanically ventilated patient. Right heart catheterization has been the gold standard for diagnosis of pulmonary hypertension. Our patient had right heart catheterization four months after her initial COVID-19 infection due to persistent dyspnea.

CONCLUSION

This revealed new onset PAH that developed following her infection with COVID-19, an emerging sequela of the infection

Key Words: Pulmonary arterial hypertension post COVID-19 infection; PAH after COVID-19 infection; COVID-19 induced Pulmonary arterial hypertension diagnosed with right heart catheterization; Pulmonary arterial hypertension; Pulmonary arterial hypertension; Right heart catheterization; Right heart catheterization; COVID-19

Core Tip: Pulmonary arterial hypertension has been reported in literature as a cardiovascular complication of coronavirus disease 2019 (COVID-19). To our knowledge, this is the first case report of pulmonary arterial hypertension confirmed by right heart catheterization in a non-ventilated patient following infection with COVID-19 complicated by hypoxic respiratory insufficiency.

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INTRODUCTION

This case highlights pulmonary arterial hypertension (PAH) as a potential pulmonary-vascular complication of coronavirus disease 2019 (COVID-19).

CASE PRESENTATION

Chief complaints

A 71-year-old African American woman with a history of hypertension, chronic renal impairment and hyperlipidemia presented to the emergency department (ED) with fatigue, non-productive cough and mild dyspnea for a few days. She denied fever, myalgias, headaches, vomiting or diarrhea.

History of present illness

She worked at a medical facility and reported possible exposure to COVID-19 while at work.

History of past illness

She had no history of pulmonary disease, cardiac problems, venous thromboembolism, or sleep apnea. She denied smoking or use of illicit drugs.

Personal and family history

She also reported no family history of dyspnea.

Physical examination

On examination, her temperature was 98.4 F, pulse 73/min, blood pressure (BP) 118/74, respiratory rate 17/min and oxygen saturation 96% on room air. She had bibasilar crackles on chest auscultation with otherwise normal exam findings.

Laboratory examinations

Labs revealed a normal blood cell count, creatinine 2.08 mg/dL, N-terminal fragment of B-type natriuretic peptides 57 pg/mL, Troponin-T < 0.01 ng/mL and normal urinalysis.

Imaging examinations

Electrocardiographic showed normal sinus rhythm with no abnormalities. Her chest X-ray showed patchy opacities in the right lung with no pleural effusions.

FINAL DIAGNOSIS

She was COVID-19 tested, and initially discharged home on azithromycin with a subsequent positive test result two days later.

Seven days after her initial ED visit, she experienced worsening shortness of breath (SOB) and called 911. Emergency medical personnel, noting an oxygen saturation of 80%, placed her on supplemental oxygen at 2 L/min and transported her to the ED. There she reported severe SOB, a non-productive cough, loss of taste, and diarrhea. She denied fever, chest pain, or leg swelling.

Vitals revealed temperature 97.6 F, pulse 85/min, BP 94/71, respiratory rate 21/min with oxygen saturation 91% on 2 L/min *via* nasal cannula. On examination she had crackles bilaterally over the lung fields with an otherwise unremarkable exam.

Her labs revealed white blood cell count 9.47 × 10^9/L, creatinine 1.23 mg/dL, lactic acid 1.5 mmol/L, procalcitonin 0.13 ng/mL, C-reactive protein 8.4 mg/dL, D-dimer 521 ng/mL with D-Dimer 392 ng/mL, ferritin 1585 ng/mL. Repeat CXR found increased patchy opacities in both lungs. Renal impairment prevented use of chest computed tomography (CT) angiography to assess for an acute pulmonary embolism and a lung scan was not pursued given her lung opcacities which rendered that form of testing unreliable.

TREATMENT

She was admitted and placed on Levaquin for possible superimposed bacterial community-acquired pneumonia, vitamin C, and thiamine. Blood cultures showed no growth of any bacterial organisms, so antibiotics were discontinued. She improved clinically, was weaned off oxygen, and discharged home six days after admission.

OUTCOME AND FOLLOW-UP

Two weeks post-discharge, during out-patient follow-up with pulmonary medicine she reported persistence of fatigue, a predominantly nocturnal non-productive cough, and SOB episodes.

Pulmonary function test (PFT) revealed mild restrictive changes with no evidence of airway obstruction. The diffusing capacity was normal after adjusting for alveolar volume.

Transthoracic echocardiogram revealed normal left ventricular systolic function with mild diastolic dysfunction and normal left atrial pressure. Right ventricular systolic function was normal, but there was moderate tricuspid regurgitation and moderate pulmonary hypertension (PH), with an estimated right ventricular systolic pressure of 50 to 55 mmHg.

A six-minute walk test (6MWT) revealed no evidence of exercise desaturation on room air and she ambulated 708 feet during the test.

Right heart catheterization (RHC) was scheduled to further evaluate her PH, but was initially postponed due to a positive repeat COVID-19 test done prior to the procedure (2.5 mo after her initial COVID-19 diagnosis).

This was finally performed four months after initial COVID-19 positive test and revealed mild PAH Table 1.

A lung perfusion scan, to assess chronic thromboembolic pulmonary hypertension, revealed no evidence of acute or chronic pulmonary embolism. CT chest, to assess for interstitial pulmonary parenchymal abnormalities, showed clear lung fields with complete resolution of previous COVID-related lung opacities.

Patient was given the option to start Sildenafil however, given the fact that her pulmonary hypertension was mild at the time, the patient opted for watchful waiting and declined initiation of therapy. Patient was then referred to pulmonary rehabilitation following which her functional capacity improved slightly. She made the decision to retire early due to concerns of being re-exposed to COVID in the workplace.

DISCUSSION

COVID-19 has been associated with a number of cardiovascular complications including dysrhythmias, myocarditis, acute myocardial infarction, and venous thromboembolic events[1]. Several cases of PH related to COVID-19 have now been reported[2-5], however, in the majority of cases, the diagnosis was based on echocardiography data without confirmation *via* RHC which is the gold standard. Data on hemodynamics in COVID-19 patients on mechanical ventilation has also been published[6].

To our knowledge, this is the first case of PAH confirmed by RHC in non-mechanically ventilated patient following infection with COVID-19.

Table 1 Right heart catheterization data obtained in patient post-coronavirus disease 2019

	Measured values	Normal values
Right atrial pressure	5 mmHg	0-7 mmHg
Right ventricular pressure, systolic/diastolic	40/2 mmHg	45/2 mmHg
Pulmonary artery pressure, systolic/diastolic (mean)	37/14 (25) mmHg	25/12 (16) mmHg
Pulmonary capillary wedge pressure	8 mmHg	6-12 mmHg
Pulmonary vascular resistance	5 Wood Units (418 Dynes.sec.cm^{-5})	< 3 Wood Units (< 250 Dynes.sec.cm^{-5})
Transpulmonary gradient	17 mmHg	< 12 mmHg
Fick cardiac output	3.25 L/min	4.8–7.3 L/min
Cardiac index	1.79 L/min/m^2	2.8–4.2 L/min/m^2

PAH is defined as a mean pulmonary artery pressure > 20 mmHg measured *via* RHC with a pulmonary artery wedge pressure < 15 mmHg and pulmonary vascular resistance > 3 units[3,7].

Mechanisms in which new onset PAH develop in the setting of COVID-19 could be multifactorial. Interstitial and alveolar inflammation can lead to extensive pulmonary damage (group 3)[8]. COVID-19 induced endothelial injury[9], microvascular pulmonary thrombosis[10] and hypoxic vasoconstriction [11] could also lead to alterations in pulmonary vasculature (group 4). SARS-COV-2 spike protein has been associated with pulmonary vascular remodeling seen in development of new PAH after COVID-19 infection[12-14].

In addition, positive end-expiratory pressure used in mechanical ventilation increases pulmonary vascular resistance[15], leading to changes in right ventricular function[16,17]. Therefore, the measurement of pulmonary pressures *via* right heart catheterization in mechanically ventilated patients may be falsely elevated[6].

Risk factors for COVID-19 patients developing new onset PAH include a history of cardiac disease[5, 18].

Like in our patient, symptoms of COVID-19 induced PAH include persistent dyspnea, cough and fatigue[3]. Our patient continued to experience exertional dyspnea after resolution of her acute COVID-19 illness. This was in spite of resolution of her bilateral lung opacities on imaging and normal PFT and 6MWT studies. Prior to diagnosis with COVID-19, our patient was employed full-time and was very active with no dyspnea.

PAH development after COVID-19 infection can lead to a more severe course of illness[19] and increased mortality[5]. It has been hypothesized that it can be managed with medications such as endothelin receptor antagonists, phosphodiesterase five (PDE-5) inhibitors and prostacyclin, all of which are have been used to treat persons with group 1 PH (PAH)[8,19,20]. However, none of these drugs have been studied in sufficiently powered randomized clinical trials in this specific PAH population[8]. It is also currently unknown whether treatment could reverse the course of this form of PAH.

PAH related to infections is not an uncommon phenomenon. Worldwide, the most common cause of PAH is schistosomiasis[21], and the prevalence of PAH in the human immunodeficiency virus population is 100 to 1000 times greater than in the general population[22-31].

CONCLUSION

Development of PAH following infection with COVID-19 is an emerging area that deserves more investigation. Physicians and healthcare providers should have a reasonable level of suspicion for new onset PAH following COVID-19 and subsequently investigate patients presenting with persisting dyspnea following resolution of acute COVID-19 infection.

FOOTNOTES

Author contributions: Henriques King M, Ogbuka IC, and Bond VC contributed equally to this work; All authors have read and approve the final manuscript.

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