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REVIEW

COVID-19 and pulmonary fibrosis: therapeutics in clinical trials, repurposing, and potential development

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Abstract In 2019, an unprecedented disease named coronavirus disease 2019 (COVID-19) emerged and spread across the globe. Although the rapid transmission of COVID-19 has resulted in thousands of deaths and severe lung damage, conclusive treatment is not available. However, three COVID-19 vaccines have been authorized, and two more will be approved soon, according to a World Health Organization report on December 12, 2020. Many COVID-19 patients show symptoms of acute lung injury that eventually leads to pulmonary fibrosis. Our aim in this article is to present the relationship between pulmonary fibrosis and COVID-19, with a focus on angiotensin converting enzyme-2. We also evaluate the radiological imaging methods computed tomography (CT) and chest X-ray (CXR) for visualization of patient lung condition. Moreover, we review possible therapeutics for COVID-19 using four categories: treatments related and unrelated to lung disease and treatments that have and have not entered clinical trials. Although many treatments have started clinical trials, they have some drawbacks, such as short-term and small-group testing, that need to be addressed as soon as possible.

Keywords Pulmonary fibrosis · COVID-19-induced lung damage · Radiological imaging method · Angiotensin converting enzyme-2 · Possible therapeutics

Introduction

Coronavirus disease 2019 (COVID-19) is a disease caused by infection with a novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Due to its high transmissibility, approximately 4,880,000 people have been infected with SARS-CoV-2, and millions of people have died (1,900,000 dead as of January 8, 2021).

The symptoms of COVID-19 infection are generally nonspecific and include fever, dry cough, shortness of breath, and myalgia and are generally related to inflammation of the lower respiratory tract (Lechowicz et al. 2020). Radiological findings from computed tomography (CT) and chest X-ray (CXR) show that the affected pulmonary lobes of COVID-19 patients contain patchy ground-glass opacities (GGOs), fibrous stripes, and irregular solid nodules. Clinically, SARS-CoV-2 infection causes acute lung injury and eventual pulmonary fibrosis, but some aspects of COVID-19 pathogenesis remain unclear (Hadjicharalambous and Lindsay 2020).

In this article, we summarize the causes and molecular mechanisms of pulmonary fibrosis and compare them with those of COVID-19 patients, with a focus on angiotensin converting enzyme-2 (ACE2). We also review radiological imaging methods, CT and CXR, for visualizing the pathophysiology of patient lungs, as well as drugs in clinical use and clinical trials. Given that lung fibrosis is associated with COVID-19, treatments for pulmonary fibrosis are being proposed as treatments for COVID-19, and compounds used to treat other diseases have been suggested as cures for COVID-19. We classify potential treatments based on their relation to lung disease and whether a clinical trial is in process.

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Molecular mechanisms of pulmonary fibrosis

As summarized in Fig. 1, pulmonary fibrosis is characterized by irreversible scarring and remodeling of the lung and can occur in progression of several lung disorders. Some interstitial lung diseases, for example non-specific interstitial pneumonia, autoimmune-featured interstitial lung disease, and idiopathic pulmonary fibrosis, have a similar onset to COVID-19-induced pulmonary fibrosis. Among them, idiopathic pulmonary fibrosis, a specific form of pulmonary fibrosis with an unknown etiology (Sundarakrishnan et al. 2018), is a chronic and progressive lung disease that leads to irreversible remodeling of lung structure (Selman et al. 2001). Environmental (e.g., smoking, toxic dust, viral infection), microbial, genetic, and epigenetic (e.g., hypomethylation, telomerase, miRNA) factors can damage the alveolar epithelium (Coward et al. 2010; Evans et al. 2016; Chioma and Drake 2017).

Injury to the lung promotes proliferation and activation of type 2 alveolar epithelial cells (AEC2) (Shannon and Hyatt 2004) to cover the exposed alveolar surface and activates provisional matrix (Chambers 2008). In the normal repair process, the provisional matrix slowly disperses, and the lung regains its normal structure and function (Hadjicharalambous and Lindsay 2020). Type 1 alveolar epithelial cells (AEC1) make up 90% of the alveolar surface. When AEC1s are injured, AEC2s undergo apoptosis and differentiation into AEC1s to re-establish the alveolar epithelium (Selman and Pardo 2006). However, when injury is extensive, AEC2s cannot adequately re-establish the epithelium (Hadjicharalambous and Lindsay 2020), resulting in abnormal tissue repair followed by fibroblast activation, collagen deposition, connective tissue deposition, and angiogenesis (Parimon et al. 2020; Selman and Pardo 2020).

Environmental, microbial, genetic, and epigenetic factors can damage the alveolar epithelium, inducing recurrent microinjuries to lung epithelia and causing an imbalance between profibrotic (e.g., transforming growth factor-β [TGF-β], platelet-derived growth factor [PDGF], basic fibroblast growth factor, interleukin-1 [IL-1], tumor necrosis factor-α [TNF-α]) and antifibrotic (e.g., keratinocyte growth factor, hepatocyte growth factor, Extracellular biopolymers)

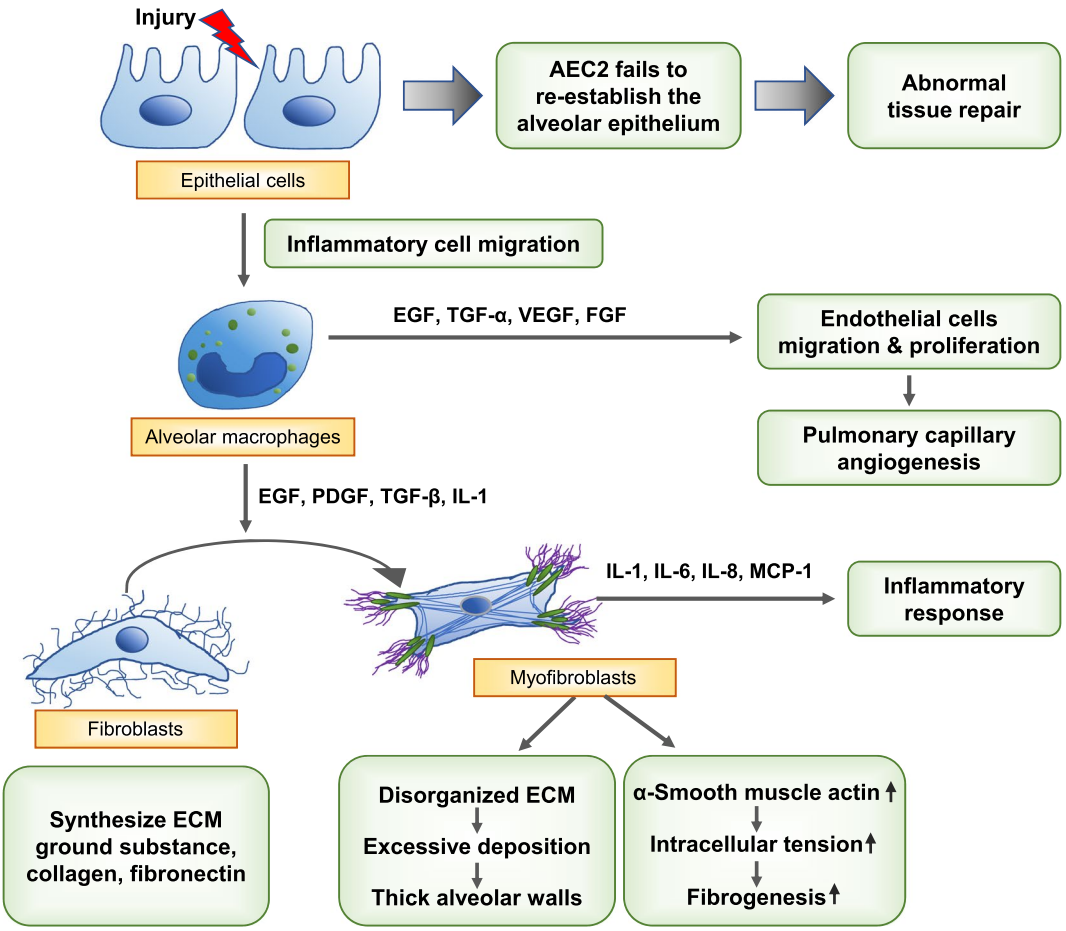

Fig. 1 Summary of pulmonary fibrosis mechanisms

mediators, which disturbs regeneration of lung epithelia (Kinoshita and Goto 2019). Some cytokines and growth factors produced by alveolar macrophages play an important role in the repair process at the site of injury. The body uses proliferation of bronchiolar stem cells, stimulated by epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-α), to compensate for the damaged alveolar epithelium (Crosby and Waters 2010). The migration and proliferation of intact endothelial cells lead to pulmonary capillary angiogenesis, in which vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) play a central role (Barrientos et al. 2008).

Fibroblasts and myofibroblasts are key cell types in idiopathic pulmonary fibrosis. In the abnormal biochemical environments produced by activated epithelial and endothelial cells, fibroblasts and myofibroblasts are induced and activated to differentiate and proliferate (Upagupta et al. 2018). Fibroblasts in the alveolar interstitium synthesize ECM ground substance, collagen, and fibronectin (Kendall and Feghali-Bostwick 2014). FGF, PDGF, and TGF-β stimulate fibroblast migration to the injured site, and those fibroblasts acquire a profibrotic phenotype that is resistant to apoptosis (Yin et al. 2020).

EGF, PDGF, TGF-β, and IL-1 proliferate and differentiate fibroblasts into myofibroblasts that perpetuate the fibrotic process. Myofibroblasts secrete IL-1, IL-6, IL-8, and monocyte chemo-attractive protein-1, which influence the inflammatory response (Ojo et al. 2020). ECM produced by myofibroblasts is more disorganized than that of fibroblasts (Wipff et al. 2007; Sgalla et al. 2018). α-Smooth muscle actin enables ECM to contract irreversibly, creating one of the features of fibrogenesis: spatial reorganization of collagen fibrils (Sgalla et al. 2018; Ojo et al. 2020). Excessive deposition of ECM components, such as fibronectin, collagens, and hyaluronan, leads to thick alveolar walls that disturb gas exchange (Wynn 2011; Fernandez and Eickelberg 2012; Kolahian et al. 2016).

Pulmonary fibrosis in COVID-19: focusing on the role of ACE2

As with other coronavirus infections, acute lung injury and subsequent repair processes are observed in COVID-19 patients. In this review, we focus on ACE2, a key entry receptor for SARS-CoV-2. Because ACE2 is a potential receptor for the SARS coronavirus infections that occurred between 2002 and 2003 (Kuba et al. 2006), many studies have examined the correlation between ACE2 and pulmonary fibrosis.

The renin-angiotensin system (RAS) is important in maintaining blood pressure homeostasis and salt balance (Wigen et al. 2020). In addition, RAS helps to regulate inflammation and pulmonary diseases such as idiopathic pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease (Tan et al. 2018).

As summarized in Fig. 2, angiotensin converting enzyme (ACE), which is widely expressed in capillary blood vessels

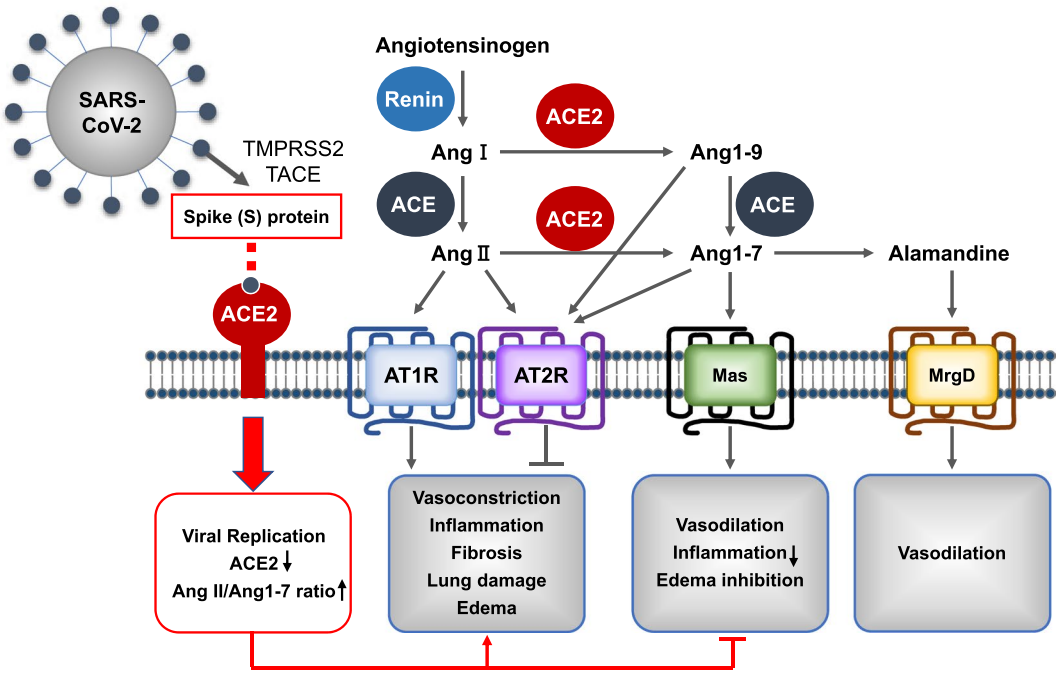

Fig. 2 Summary of ACE function in the renin-angiotensin system and how viral infection affects it

in the human lung (Studdy et al. 1983), generates octapeptide angiotensin II (Ang II) from decapeptide angiotensin I (Ang I) by cleaving dipeptides from the C-terminus (Corvol et al. 1995; Skeggs et al. 1980). ACE also generates angiotensin 1–7 (Ang 1–7) from angiotensin 1–9 (Ang 1–9). ACE2 removes a single residue from Ang I, generating Ang 1–9, and from Ang II, generating Ang 1–7 (Donoghue et al. 2000). Thus, both ACE and ACE2 function as carboxypeptidases, but they have different substrate specificity (Donoghue et al. 2000; Tipnis et al. 2000; Vickers et al. 2002). Lungs express the angiotensin II type 1 receptor (AT1R), angiotensin II type 2 receptor (AT2R), Mas receptors, and MrgD receptors (Jia 2016; Shrikrishna et al. 2012). Ang II binds to AT1R or AT2R, Ang 1–7 binds to Mas receptors (Errarte et al. 2017), and alamandine binds to MrgD receptors (Kaur et al. 2020a). Through AT1R, Ang II performs biological functions such as promoting vasoconstriction, inflammation, fibrosis, lung damage, and edema (Errarte et al. 2017). Through the Mas receptors, on the other hand, the downstream actions of Ang 1–9 or Ang 1–7 contribute to vasodilation, inflammation reduction, and edema inhibition (Errarte et al. 2017; Wigen et al. 2020). Through MrgD receptors, alamandine, which is the decarboxylated form of Ang 1–7, increases cyclic adenosine monophosphate (cAMP) in endothelial cells, and this leads to vasodilation, as in the case of activation of Mas receptors (Kaur et al. 2020a). Thus, ACE2 functions as a negative regulator of the angiotensin system (Furuhashi et al. 2020).

At the adsorption step in the viral replication cycle, the viral spike (S) protein of SARS-CoV-2 binds to membrane-anchored ACE2 of the RAS. Then, the cellular transmembrane protease serine 2 (TMPRSS2) and other related proteases, such as tumor necrosis factor-α-converting enzyme, act in S-protein cleavage, which activates the S-protein and results in viral fusion to the host cell membrane (Heurich et al. 2014; Hoffmann et al. 2020). Internalization of ACE2 by SARS-CoV-2 would significantly reduce ACE2 on the cell surface and increase the ratio of Ang II:Ang 1–7 (South et al. 2020). Moreover, the major sources of ACE2 are alveolar type 2 pneumocytes (Bombardini and Picano 2020). Repetitive viral infection of type 2 pneumocytes has a cytolytic effect that results in differentiation toward type 1 pneumocytes and active proliferation of type 1 pneumocytes to replace the damaged alveolar type 2 pneumocytes, which downregulates ACE2 expression (Delpino and Quarleri 2020). Downregulation of ACE2 suppresses the downstream protective activities of RAS, followed by inflammation and pulmonary fibrosis (Wigen et al. 2020).

The plasma level of ACE2 is increased in patients with severe COVID-19 (H. Zhang et al. 2020). Soluble ACE2 that circulates in the blood has a protective effect by binding the virus, disturbing endocytosis (Wigen et al. 2020). Increased soluble ACE2 facilitates the downstream action of Ang 1–7 to counteract inflammation and pulmonary fibrosis, while increased membrane-bound ACE2 can function as a viral entry receptor (Dalan et al. 2020; Leung et al. 2020).

Ang II is a key effector peptide of the RAS system that participates in tissue remodeling and fibrosis by promoting the expression of transforming growth factor-β1 (TGF-β1), which is a profibrotic cytokine that converts fibroblasts into myofibroblasts and deposits collagen (Weber 1997). TGF-β1 is thought to suppress antioxidant enzymes and thereby increase the ROS level, and ROS induce TGF-β1 and its fibrogenic effects (Liu and Desai 2015). Both factors are highly expressed in fibrotic processes. Thus, Ang II contributes to the pathogenesis of pulmonary fibrosis. On the other hand, ACE2 inhibits fibrosis by decreasing the amounts of TGF- β1 and α-smooth muscle actin in human lungs (Wang et al. 2015). In addition, levels of VEGF, IL-1, and IL-6 are increased in COVID-19 patients, just as they are in idiopathic pulmonary fibrosis patients (George et al. 2020).

Radiological imaging methods to diagnose COVID-19

A variety of COVID-19 diagnosis methods has been reviewed, including real-time reverse transcriptase PCR (RT-PCR) used with CRISPR-mediated detection or loop-mediated isothermal amplification techniques and antibody testing Lamb et al. 2020; Li and Ren 2020; Vandenberg et al. 2020; J. Zhang et al. 2020). We review only radiological imaging methods used to diagnose COVID-19.

Many clinicians use radiological imaging methods, especially for evaluating emergency room patients while waiting for the results of RT-PCR (Cozzi et al. 2020). The two major radiological techniques are CXR and CT. In many study cases, both are used for observing fibrotic changes in COVID-19-induced pulmonary fibrosis (Ojo et al. 2020).

Computed tomography

The reference standard for COVID-19 diagnosis is RT-PCR. According to the recent COVID-19 literature, CT is primarily being used to address the limitations of RT-PCR. For example, RT-PCR results require 5 to 6 h to obtain, whereas CT examination results are available much sooner. Moreover, a CT examination can help in early diagnosis of asymptomatic COVID-19 patients and in diagnosing patients with false-negative RT-PCR results. Though RT-PCR is the gold standard for COVID-19 diagnosis, false-negative results are common (Long et al. 2020). Chest CT has high sensitivity for detecting early COVID-19 in patients with later positive conversion of RT-PCR results versus RT-PCR (98% vs. 71%, respectively) (Fang et al. 2020). CT examinations can be used to evaluate therapeutic efficacy and monitor disease

progression (Ye et al. 2020) because COVID-19 patients with different disease courses and severity show different CT imaging features and patterns. Several COVID-19 case studies have reported typical and atypical CT manifestations: Typical CT symptoms include GGO, consolidation, a reticular pattern, and a crazy paving pattern, whereas relatively atypical CT symptoms are airway changes, pleural changes, a subpleural curvilinear line, fibrosis, vascular enlargement, air bubble sign, nodules, halo sign, reversed halo sign or atoll sign, lymphadenopathy, and pericardial effusion (Ye et al. 2020). Among those symptoms, GGO and consolidation are commonly used for COVID-19 diagnosis, but CT manifestations vary and change over the course of the disease (Okamori et al. 2020).

Chest X-ray

Although CT has better sensitivity and specificity than CXR, CT has some problems, such as radiation exposure and complex scanner disinfection procedures (Cozzi et al. 2020). On the other hand, CXRs are inexpensive, faster, more widespread, and have a low risk of patient exposure to radiation (Self et al. 2013; Rubin et al. 2020). Therefore, CXR is another useful diagnostic method. The Italian Society of Radiology recommended CXR as a first-line imaging tool (Giovagnoni 2020; Neri et al. 2020), and the American College of Radiologists recommends using portable CXR to decrease the risk of cross infection because the COVID-19 virus has a high infection rate (Rousan et al. 2020).

Many COVID-19 patients show abnormal CXR findings, including peripheral GGO in the lower lobes, consolidation, septal thickening, lymphadenopathy, bronchiectasis, cavitation, and pleural effusion (Bernheim et al. 2020; Caruso et al. 2020; Meng et al. 2020; Salehi et al. 2020; Wong et al. 2020; Yoon et al. 2020).

CXR findings might not reflect early or mild disease (Kim et al. 2020); therefore, normal CXR results do not necessarily rule out COVID-19 infection. Instead, CXR can be used to classify the highest risk patients who will most benefit from hospitalization in an area that lacks hospital beds due to a surging number of patients (Kim et al. 2020).

Therapeutics

Pharmacological approaches with subdivisions

Drugs for lung diseases being tried in clinical trials for COVID-19

Propolis Propolis can be correlated with immune system defenses, reduced viral replication, and anti-inflammatory action in SARS-CoV-2 (Ansorge et al. 2003; Shimizu et al. 2011; Machado et al. 2012; Chan et al. 2013; Hori et al. 2013). Propolis extract and its components can act as an anti-COVID-19 drug by reducing TMPRSS2 expression and ACE2 anchorage (Kaur et al. 2020a, b). They also immunomodulate monocytes and macrophages by reducing or eliminating IL-1β and IL-6. In addition, they reduce transcription factors such as NF-κB and JAK2/STAT3 (Shimizu et al. 2011; Asgharpour et al. 2019; Güler et al. 2020; Omar et al. 2020). NF-κB inhibition blocks the production of cytokines in T cells and reduces JAK2/STAT3 signaling, which diminishes inflammation and oxidative stress (Ansorge et al. 2003; Fernandes et al. 2015). Substances found in several types of propolis, caffeine phenethyl ester (CAPE), galangin, chrysin, and caffeic acid, have been shown to inhibit the 3-chymotrypsin-like cysteine enzyme, which is an essential protease for SARS-CoV-2 (Hashem 2020; Kumar et al. 2020). In addition, the Rac protein could be inactivated by CAPE, a component of propolis. Rac inactivation leads to PAK1 inhibition, which represses B cells and T cells. PAK1 is a kinase that is increased during lung inflammation and lung fibrosis (Berretta et al. 2020). PAK1 inhibitors can rescue the immune system and help fight against viruses (Xu et al. 2005; Gorbalenya et al. 2020; Maruta and He 2020). Propolis and its components can help prevent immunosuppression during the initial phases of the disease and decrease the excessive inflammatory response of the host by blocking excess IL-6, IL-2, and JAK signaling in later stages (Nile et al. 2020). One study reported that the use of propolis water extract can reduce the expression of pro-inflammatory cytokines such as TNF-α, ICAM-1, IL-6, and IL-8 and increase the protective cytokine IL-10 (Qin et al. 2020). These benefits of propolis have triggered a clinical trial of Brazilian green propolis extract for treatment of COVID-19 patients in Brazil (https://clinicaltrials.gov/ct2/ show/NCT04480593) (Berretta et al. 2020).

CD147 inhibitor CD147 is a receptor for SARS-CoV-2 host cell invasion (K. Wang et al. 2020; Yan et al. 2020). Therefore, a phase 2 clinical trial to prevent COVID-19 by blocking CD147, and thereby entry of the virus, is underway in China (Ulrich and Pillat 2020). The study is testing a humanized form of anti-CD147, Meplazumab, which is specific for CD147, suggesting that CD147 could be a target for preventing COVID-19 (K. Wang et al. 2020). A relationship has been reported between CD147 upregulation and conditions such as diabetes and asthma, so Meplazumab might also prevent diabetes and its complications (Bao et al. 2010; Moheimani et al. 2018). CD147 exists in several types of pulmonary cells, including type 2 pneumocytes and macrophages at the edge of fibrotic regions. Anti-CD147 antibodies block the differentiation and proliferation of fibroblasts into myofibroblasts that are induced by TGF-β1 (Guillot et al. 2006). Thus,

blocking CD147 could prevent pulmonary fibrosis caused by COVID-19 (Ulrich and Pillat 2020).

Low-molecular weight heparin (LMWH) LMWH treatment for COVID-19 is in randomized clinical trials (NCT04366960). Coagulation and D-dimers can determine the severity of the pulmonary diseases that follow COVID-19 infection (Di Perri 2020). In some studies, patients taking heparin had lower mortality rates and higher level of D-dimer than control patients (Beigel et al. 2020). Heparin also blocks SARS-CoV-2 from binding to the ACE2 receptor and downregulates IL-6, which can trigger the cytokine storm (Mummery and Rider 2000; Atallah et al. 2020; Kaur et al. 2020a). Dosing and timing are controversial, but the clinical trials currently underway might clarify these aspects (Di Perri 2020).

Montelukast Montelukast, which strongly antagonizes the cysteinyl leukotriene receptor, is in clinical trial for COVID-19 treatment (NCT04389411). It has anti-inflammatory effects and can block the function of cysLT, such as the cytokine production that is one of the main features of COVID-19 infection (Fidan and Aydoğdu 2020). Some montelukast results (high doses, i.v. administration) show a decrease in protein expression of cysteinyl leukotriene, IL-4, IL-5, and IL-13 in the lungs and an anti-inflammatory effect caused by down-regulation of T-helper 2 cytokines. The anti-inflammatory effect of high-dose montelukast has been demonstrated in asthma (Wu et al. 2003). Montelukast also blocks bradykinin-induced airway hypersensitivity, which causes a cough associated with ACE inhibition. The mechanism remains uncertain, but it is thought to affect the production of the ACE receptor, which is a receptor for SARS-CoV-2 (Bisgaard et al. 2008; Noor et al. 2011; Kaur et al. 2020a). Therefore, montelukast could be an effective therapeutic for COVID-19.

Phosphodiesterase (PDE) inhibitors PDE5 inhibitors such as sildenafil could be a targeted treatment for COVID-19 and other lung diseases. PDE5 is primarily expressed in the lungs (Giorgi et al. 2020; Isidori et al. 2020). PDE5 inhibition can reduce the cytokine storm by reducing the release of pro-inflammatory cytokines because it can downregulate angiotensin II receptor type 1 (AT-1) receptor (Isidori et al. 2020). PDE5 inhibitors are safe and have some benefits in type 2 diabetes patients, such as reducing disease-related mortality (Giannetta et al. 2014). Sildenafil can prevent clotting and thrombotic complications by blocking the transformation of endothelial and smooth muscles into mesenchymal cells in pulmonary arteries (Isidori et al. 2020). The clinical trial process for the use of PDE5 inhibitors in COVID-19 treatment could be facilitated by the various clinical trials already conducted for PDE5 inhibitors in a variety of diseases (Phillips 2020).

Drugs for other diseases being tired in clinical trials of COVID-19

Novavax A phase III trial of NVX-CoV2373 (Novavax), a recombinant SARS-CoV-2 nanoparticle vaccine, recently has started in the UK (Du et al. 2009; Keech et al. 2020; Tai et al. 2020). Novavax contains the trimeric full-length spike glycoproteins of SARS-CoV-2 and the adjuvant Matrix-M1 (Du et al. 2009; Giannetta et al. 2014; Bengtsson et al. 2016; Chen et al. 2020; Giorgi et al. 2020; Isidori et al. 2020; Keech et al. 2020; Phillips 2020; Tai et al. 2020). Novavax blocks SARS-CoV-2 infection in rodent and other non-human models by inducing a high titer of antibody IgG, which inhibits binding to human ACE2 and neutralizes the virus (Kaur et al. 2020a). It also produces multifunctional CD4 + and CD8 + T cell responses, mainly with the T helper phenotype (Mandolesi et al. 2020; Tian et al. 2020). The protective mechanism against COVID-19 is not clear, but the neutralizing antibodies appear to be related to the protection (Mulligan et al. 2020). During phase I and II trials, no critical side effects were observed, indicating the safety of Novavax (Keech et al. 2020). Although the previous trials were small and had short follow-up periods, Novavax could be an effective vaccine against COVID-19.

Melatonin Many studies suggest that melatonin could be an effective treatment for COVID-19. Recently, a clinical trial has started in ICU patients with COVID-19 (NCT04568863) (Acuña-Castroviejo et al. 2020). The cytokine storm of COVID-19 is associated with activation of the NF-κB pathway and release of cytokines such as IL-1β (Merad and Martin 2020; Tay et al. 2020). Melatonin can act as an anti-inflammatory molecule because it can block NF-κB activation and the positive feedback of IL-1β. Studies also found that the main target of melatonin is mitochondria, and that melatonin can maintain mitochondria and homeostasis in all organs and tissues of mice with sepsis (Martín et al. 2000; Escames et al. 2003). Moreover, it can rescue the lungs from oxidative damage caused by age (Acuña-Castroviejo et al. 2012). Because the inflammatory response of sepsis is similar to that of COVID-19, melatonin could be an effective treatment for COVID-19 (Keech et al. 2020).

Remdesivir Remdesivir is a promising drug for COVID-19. Remdesivir, an adenosine analog, is changed to its active form (GS-443,902) and selectively blocks the viral RNA-dependent RNA polymerase (Lo et al. 2017; Sheahan et al. 2017; Agostini et al. 2018; Agency 2020). This drug has effects in many diseases, including SARS-CoV-1 and MERS-CoV infections (Sheahan et al. 2017, 2020; de Wit et al. 2020; Gordon et al. 2020). Some reports discuss the anti-viral and clinical effects of remdesivir (Singh et al. 2020). In addition, remdesivir can inhibit epithelial cells in human nasal and bronchial airways (Pizzorno 2020). Due to its many effects and efficacy, the United States Food Drug

Administration has granted an Emergency Use Authorization to remdesivir for COVID-19 treatment (Singh et al. 2020). However, many clinical trials are ongoing, and its safety must be validated.

Chloroquine and hydroxychloroquine Chloroquine and hydroxychloroquine can be used to treat COVID-19 (Meo et al. 2020). Chloroquine increases endosomal pH and inhibits virus-cell fusion and viral infection. It also blocks virus-cell binding by inhibiting glycosylation of SARS-CoV receptors (Vincent et al. 2005). Many clinical trials have examined their safety and efficacy. Chloroquine can shorten disease progression by blocking degeneration to pneumonia, enhancing lung imaging findings, and accelerating virus-negative conversion (Gao et al. 2020). However, *in vitro* studies have shown that hydroxychloroquine is more effective than chloroquine at inhibiting SARS-CoV-2 (Yao et al. 2020). The United States Food Drug Administration permits the use of hydroxychloroquine and chloroquine to treat COVID-19 (Diamond 2020).

BTK/ITK dual inhibitors Bruton's tyrosine kinase (BTK)/inducible T-cell kinase (ITK) dual inhibitors can treat COVID-19 (McGee et al. 2020). COVID-19 patients have elevated levels of blood neutrophils and cytokines, and inhibiting that immune response can be therapeutic (D. Wang et al. 2020). BTK, which is prevalent in B cells, elevates proinflammatory cytokines, including IFN-β, by means of various signaling pathways for TLRs, macrophages, and dendritic cells (Weber et al. 2017). In patients with severe COVID-19, NF-κB is elevated, which mediates the TLR/BTK signaling pathway (Liao et al. 2020). BTK also is associated with production of inflammatory cytokines, such as active pro-IL-1β (Weber et al. 2017). Therefore, the BTK inhibitors acalabrutinib, zanubrutinib, and ibrutinib are in clinical trials as treatments for COVID-19. Also, ITK, which is prevalent in T cells, modulates activation of CD4 + and CD8 + T cells and production of cytokines (Solouki et al. 2019). Some studies suggest that the Th1 response is important in regulating respiratory coronaviruses because Th1-polarized SARS-CoV-2-specific memory T cell responses are observed in COVID-19 patients (Dong et al. 2020; Grifoni et al. 2020; Neidleman et al. 2020; Weiskopf 2020). ITK signaling results in elevation of the Fas ligand (FasL), which leads to activation-induced T cell death (Long et al. 2017). Inhibition of ITK signaling elevates the level of CD4 + T cells and is effective for treating COVID-19 (Sun et al. 2015).

Potential drugs for COVID-19 not yet in clinical trials

Galectin-3 (Gal3) inhibitors One of the principle phases of COVID-19 is the hyperinflammatory phase, during which immune cells release gal3 (Burguillos et al. 2015; Boza-Serrano et al. 2019). There have been reports of elevated gal3 level in proliferative T cells in patients with COVID-19 (Liao et al. 2020). Gal3 is a carbohydrate-binding protein expressed by macrophages and epithelial and alveolar cells in the lungs (Reyfman et al. 2019). Gal3 binds to and activates TLR4 and TREM2, reflecting its association with lung diseases and fibrosis (Burguillos et al. 2015; Boza-Serrano et al. 2019). TREM2, expressed by macrophages, is a marker related to the fibrotic process (Liao et al. 2020), and TLR, which is critical for antiviral response, leads to strong inflammation associated with interferon-related genes, interleukins, chemokines, and gal3 expression (Guo et al. 2020). Some gal3 inhibitors have been shown to suppress the release of IL-1, IL-6, and TNF-α, which are related to the inflammatory phase of COVID-19 (Boza-Serrano et al. 2014, 2019). Gal3 shares an extracellular domain with ACE2, the receptor for SARS-CoV-2 infection, indicating that gal3 inhibitors bind to ACE2 (Clarke and Turner 2012; Kovak et al. 2014; Kaur et al. 2020a). TD139, a gal3 inhibitor provided by Galecto Biotech, has been shown to be safe and effective against idiopathic lung fibrosis (NCT04473053), and clinical trials could be performed in the presence of a clinically tolerable gal3 inhibitor (Garcia-Revilla et al. 2020).

Poly-(ADP-ribose) polymerase inhibitor (PARPi) PARPi could be an effective treatment for COVID-19 because it can prevent cytokine storms (macrophage overactivation) and protect cells against death (Curtin et al. 2020). Previous studies have suggested that SARS-CoV-2 infection induces PARP activation, which is increased in the lung tissue of asthmatic patients, and different preclinical animal models have indicated that PARPi could reduce the lung fibrosis induced by SARS-CoV-2 lung inflammation (Ghonim, Pyakurel, Ibba, Al-Khami, et al. 2015; Carlile et al. 2016). The cytokine storm, a major reason for mortality in COVID-19, results in multi-organ failure (Mehta et al. 2020). Many studies in animal models suggest that PARPi, including olaparib, can reduce IL-6 and IL-1β expression in many organs, including the lungs (Mabley et al. 2001; Liaudet et al. 2002; Pagano et al. 2007; Kim et al. 2008; Ghonim, Pyakurel, Ibba, Wang, et al. 2015; Sethi et al. 2019; Sahu et al. 2020). Moreover, olaparib has been shown to reduce the level of TNF-α in the lungs in animal models of lung inflammation (Cuzzocrea et al. 2002; Liaudet et al. 2002; Virág et al. 2004; Kim et al. 2008; Sahu et al. 2020). These preclinical studies and results show that PARPi has potential for human applications as a notable potential treatment for COVID-19.

Cobra venom and NNAV Cobrotoxin and α-neurotoxin from *Naja naja atra* venom (NNAV) can be used to prevent and relieve symptoms of COVID-19. Cobrotoxin and α-neurotoxin have many pharmacodynamic actions through their binding to nicotinic acetylcholine receptors, which are widely distributed throughout the body (Kuo et al. 1995;

Lin et al. 2020). NNAV and α-neurotoxins can inhibit the cytokine storm through their strong inhibitory effects on inflammation (Lin et al. 2020; L. Zhang et al. 2020). NNAV and cobrotoxin also have immunoprotective activity. CD8 T cells are increased in COVID-19 patients and their proliferation can be blocked by NNAV and cobrotoxin more than they affect CD4 T cells. NNAV and cobrotoxin also restore the CD4/CD8 ratio (Ganji et al. 2020; Lin et al. 2020). can inhibit lung inflammation, improve lung gas exchange function, and reduce the development of fibrotic lesions in the lung (George et al. 2020; Polak et al. 2020). Cobra venoms were first approved for use by the US Food and Drug Administration in the 1940 s (Lin et al. 2020).

Tetracyclines Tetracyclines, which are lipophilic antibiotics, may be effective for treating COVID-19. Tetracyclines can permeate lung tissue and might block SARS-CoV-2 replication in the lungs through their anti-inflammatory effects (Sodhi and Etminan 2020). Chemically modified tetracyclines are used to prevent septic shock caused by ARDS, which is a main complication in COVID-19 patients (Griffin et al. 2010). Also, the host matrix metalloproteinase (MMP) complex, which includes zinc, plays an important role in coronavirus survival and cell penetration, adherence, and replication (Humar et al. 2004; Phillips et al. 2017). Tetracyclines can chelate the zinc compounds on MMPs, which can inhibit SARS-CoV-2 replication in the host (Zakeri and Wright 2008). Furthermore, inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are increased in patients with severe SARS-CoV-2 (Yoshikawa et al. 2009). The elevation of those cytokines can be inhibited by tetracyclines through NF-κB pathway suppression, so they can be therapeutics for COVID-19 (Henehan et al. 2017).

Saikosaponins Saikosaponins, especially saikosaponin A, saikosaponin B, and saikosaponin D, are potential treatments for COVID-19 (Bahbah et al. 2020). Saikosaponins have antiviral effects on various viruses. Saikosaponin A decreases the immunopathology of the lung, and saikosaponin B blocks HCoV-229E infection *in vitro* by inhibiting viral adherence and invasion into cells (Cheng et al. 2006). The immunomodulatory and anti-inflammatory activities of saikosaponin A might block increases in inflammatory mediators and cytokines, such as TNF-α, COX-2, and interleukins, which are found in patients with severe COVID-19 (Yuan et al. 2017). Moreover, saikosaponin A binds highly to the ACE-2 receptor, which is the main receptor for SARS-CoV-2 infection (Kaur et al. 2020a; Yan et al. 2020).

Non-pharmacological approaches

Extracorporeal membrane oxygenation (ECMO) A case report described how a 31-year-old pregnant woman at 35 weeks of gestation received ECMO treatment and was cured of COVID-19 infection (Hou et al. 2020). ECMO improves gas exchange and relieves ventilator-associated lung injury in acute respiratory distress syndrome (ARDS) treatment, so use of ECMO can temporarily restore pulmonary function (Davies et al. 2009). However, the role of ECMO in COVID-19 patients with respiratory failure remains unclear. Many COVID-19 patients who were treated with ECMO have died (X. Li et al. 2020). The leading causes of death in COVID-19 patients are bleeding and infection, which lead to lymphocyte and IL-6 elevation (Henry 2020; Henry and Lippi 2020). Although ECMO has some safety issues, it can ameliorate lung dysfunction, and one case report shows its potential for treating COVID-19 patients.

Stem cells Stem cell therapy, especially mesenchymal stem cell (MSC)-related therapy, could be a treatment for COVID-19. MSCs have anti-inflammatory signaling and immunomodulatory properties, making them effective against diseases such as COVID-19 (Z. Li et al. 2020). The immunomodulatory ability of MSCs can reduce the cytokine storm and prevent the T cell imbalance caused by COVID-19 infection (Uccelli and de Rosbo 2015; Fayyad-Kazan et al. 2016; Leng et al. 2020). MSCs also act on antigen-presenting cells such as dendritic cells and macrophages, modulating ARDS, anti-viral immunity, and tissue healing in COVID-19 patients (Z. Li et al. 2020; Merad and Martin 2020; Zhou et al. 2020). Clinical trials of stem cell therapies for COVID-19 are ongoing in many countries. The results from preclinical and early clinical studies have demonstrated their efficacy and direct MSC relocation to the lungs, which could help treat pulmonary diseases in patients with COVID-19. However, the safety and efficacy of stem cell therapy should be further demonstrated through continuing clinical studies (Z. Li et al. 2020).

Clustered regularly interspaced short palindromic repeats (CRISPR) CRISPR, which is a tool for gene editing, can be used as a COVID-19 treatment (Straiton 2020). Its editing tool can be applied to block SARS-CoV-2 replication and induce damage to the viral RNA. Also, prophylactic antiviral CRISPR in human cells (PAC-MAN) contains a gRNA strand that is particular to SARS-CoV-2 genome nucleotide sequences (Abbott et al. 2020). Still, there are many problems to solve, the most challenging of which is delivery of its bulky components into cells (Kobie 2020). Synthetic, nontoxic peptide lipitoids are a possible solution to this because they can encapsulate nucleotides as nanoparticles. When lipitoids and PAC-MAN technology were combined, they decreased the SARS-CoV-2 level in a sample of human epithelial lung cells by more than 90% (Laboratory 2020). More studies are required, but existing results reflect the potential of CRISPR as a treatment for COVID-19.

Conclusions

COVID-19 is an unprecedented disease that spreads rapidly and has caused many infections and deaths worldwide. Many COVID-19 patients suffer lung damage, including pulmonary fibrosis in severe cases. We described the causes and molecular mechanisms of pulmonary fibrosis and compared them with reports about SARS-CoV-2 patients. We specifically focused on the relationship between ACE2 and pulmonary fibrosis in COVID-19 patients. In many COVID-19 patients, decreased ACE2 expression is observed, which leads to decreased Ang 1–7 levels and increased Ang II activity, which can produce pulmonary fibrosis (Delpino and Quarleri 2020). Although the molecular mechanisms of pulmonary fibrosis in COVID-19 patients remain unclear, the involvement of ACE2 is promising.

We reviewed the use of radiological imaging methods CT and CXR to show the pathophysiology of patient lungs, and we inferred that they can be used for diagnosing lung diseases in COVID-19 patients.

We also provided an overview of some therapeutics for COVID-19 patients. We classified treatments as those related or unrelated to lung diseases and those that have or have not entered clinical trials. Many therapeutics are in clinical trials and showing good potential as COVID-19 treatments, and many of those are used to treat other diseases. However, even in previously approved treatments, dosing, safety, and efficacy for COVID-19 patients should be clearly identified. Clinical trials with larger populations and longer periods are needed to verify effectiveness and safety. A great deal of further research is needed, but we expect the detailed mechanisms of SARS-CoV-2 to be elucidated soon.

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Declarations

Conflict of interest The authors have no conflicts of interests to declare.

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