LITERATURE REVIEW

Role of Nintedanib in COVID-19-Related Lung Fibrosis

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ABSTRACT

In December 2020, Indonesia was introduced to the long Coronavirus disease 2019 (COVID-19) phenomenon. The Centers for Disease Control and Prevention (CDC) introduced the term "post-COVID condition" as a health problem that persists after four weeks from the first exposure to COVID-19. The National Institute for Healthcare and Care Excellence (NICE) classifies COVID-19 infections into three categories based on disease duration: (1) acute infection for up to 4 weeks; (2) ongoing infection within 4-12 weeks; and (3) post-COVID-19 syndrome for more than 12 weeks and not associated with an alternative diagnosis. One of these phenomena is lung fibrosis. About 80% of COVID-19 survivors had mild to severe chest X-rays in 6 months of follow-up with decreasing lung function. COVID-19-related lung fibrosis is still not widely researched. COVID-19 survivors who develop lung fibrosis usually recover independently, but some develop persistent lung fibrosis. The use of antifibrotic agents, such as nintedanib, has long been approved for idiopathic pulmonary fibrosis (IPF). However, its use in the cases of lung fibrosis due to COVID-19 has not been widely studied. Nintedanib is a tyrosine kinase inhibitor. It inhibits receptor activity of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF). Those actions will eventually inhibit the proliferation, migration, and transformation of fibroblasts into myofibroblasts in lung fibrogenesis. Therefore, an anti-fibrotic agent is potentially needed to inhibit COVID-19-related lung fibrosis to improve quality of life and prevent further lung damage.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2). This disease causes clinical manifestations in respiratory, pulmonary, and systemic complications. COVID-19 is a respiratory virus, which is virus that takes the respiratory tract as a place of entry. The virus can proliferate in the airway epithelial cells, then spreads through the pulmonary bloodstream and causes pathological changes in the lungs and tissues or organs outside the lungs.[1]

In April 2020, the Centers for Disease Control and Prevention (CDC) introduced the term "post-COVID condition", which describes a health problem that persists after four weeks from the first exposure to a COVID-19 survivor. The National Institute for Healthcare and Care Excellence (NICE) classifies COVID-19 infections into three categories based on disease duration: (1) acute infection for up to four weeks; (2) ongoing infection within 4-12 weeks; and (3) post-COVID-19 syndrome. Post-COVID-19 syndrome is characterized by signs and symptoms that develop during or after COVID-19 infection, present for >12 weeks, and are not associated with an alternative diagnosis. In the United States (US),

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several studies suggest that 10% of all COVID-19 survivors experienced a post-COVID condition phenomenon, which they call "long haulers." In most cases, COVID-19 patients experience improvement in their condition after 2–6 weeks after being infected, but some symptoms can persist or reappear weeks to months after the patient has recovered.[2–4]

One of the long-term COVID-19 symptoms is damage to the lung organs with findings of fibrosis. Lung fibrosis is the formation of scar tissue in the lung tissue around the alveoli or interstitial tissue, leading to decreased elasticity of the lungs, respiratory function, and oxygen levels in the blood. Therefore, the therapy in lung fibrosis inhibits the process of wider lung damage.[3,5] Deepandra, *et al*. showed that lung fibrosis caused by this virus differs from classical acute respiratory distress syndrome (ARDS), with the histopathological findings indicating the location of damage to alveolar epithelial cells rather than endothelial cells. This makes the difference between lung fibrosis due to COVID-19 and other lung fibrosis diseases.[6]

Nintedanib works by inhibiting intracellular tyrosine kinases and the development of lung fibrosis. It inhibits the kinase activity of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), leading to inhibition of proliferation, migration, and transformation of fibroblasts into myofibroblasts in the lung fibrogenesis.[7] There is still a lack of data on the role of nintedanib in cases of COVID-19-related lung fibrosis. Therefore, this literature review aimed to deepen our knowledge of the role of nintedanib, which has the potential to inhibit fibrosis due to COVID-19.

COVID-19-Related Lung Fibrosis and the Risk Factors

Fibrosis is the depositing of fibrotic connective tissue or scar tissue. Lung fibrosis is damage to the lung structure due to the formation of scar tissue in the lungs, characterized by the accumulation of extracellular matrix (ECM).[8] Lung fibrosis due to COVID-19 is lung structure damage due to the formation of scar tissue in the lungs caused by SARS-CoV-2 infection. Zhou, *et al*. reported that from 62 patients studied, 21 (33%) had persistent lung fibrosis after two weeks of symptom onset. Pan, *et al*. reported the features of lung fibrosis in an autopsy of a COVID-19 patient characterized by diffuse alveolar damage with areas of consolidation by ECM deposition in the alveolar cavities.[9,10]

The risk factors for lung fibrosis due to COVID-19 are elderly and the severity of the disease, including comorbidities such as hypertension, diabetes, and coronary heart disease. Other factors are the length of stay in the Intensive Care Unit (ICU), the duration under mechanical ventilator, smokers, and alcohol drinkers.[6] In the elderly, it is hypothesized that the resistance of fibroblasts and myofibroblasts to apoptosis is correlated with an increase in plasminogen activator-1 (PAI-1) as an effector of Transforming Growth Factor-Beta (TGF-β), leading to persistent lung fibrosis.[11]

Based on the World Health Organization (WHO) data, the degree of COVID-19 disease is 80% mild symptoms, 14% moderate-severe symptoms, and 6% critical symptoms. Factors associated with the degree of disease, such as hypertension, diabetes, and coronary heart disease, were also found in cases of lung fibrosis by infection with Middle East Respiratory Syndrome-Corona Virus (MERS-CoV). This was also found in cases of lung fibrosis due to COVID-19, showing a correlation between the severity of the disease and an increase in the occurrence of lung fibrosis.[11]

Length of stay in the ICU and duration under mechanical ventilation cause a ventilator-induced lung injury (VILI) due to pressure abnormalities. Ventilator volume regulation leads to damage that induces pro-inflammatory cytokines to increase the occurrence of lung fibrosis in COVID-19 survivors. In a study monitoring 27 COVID-19 patients with a history of ventilator use, 110–267 days after extubation, 23 (85%) of them developed pulmonary fibrosis.[12] Smoking is associated with oxidative stress, increased proinflammatory cytokines, and lung fibrosis. A systematic analysis by Vardavas, *et al*. suggested that smokers had 1.4 times higher risk of developing severe symptoms and 2.4 times the need for ICU or death compared to non-smokers. People who frequently consume alcohol will experience a decrease in glutathione, oxidative stress, inflammation, and TGF- β in the lungs, thereby increasing the occurrence of lung fibrosis. A meta-analysis of 13 studies showed that alcohol consumption significantly increased the risk of ARDS by increasing the expression of TGF- β, a potent fibro proliferative cytokine.[13,14]

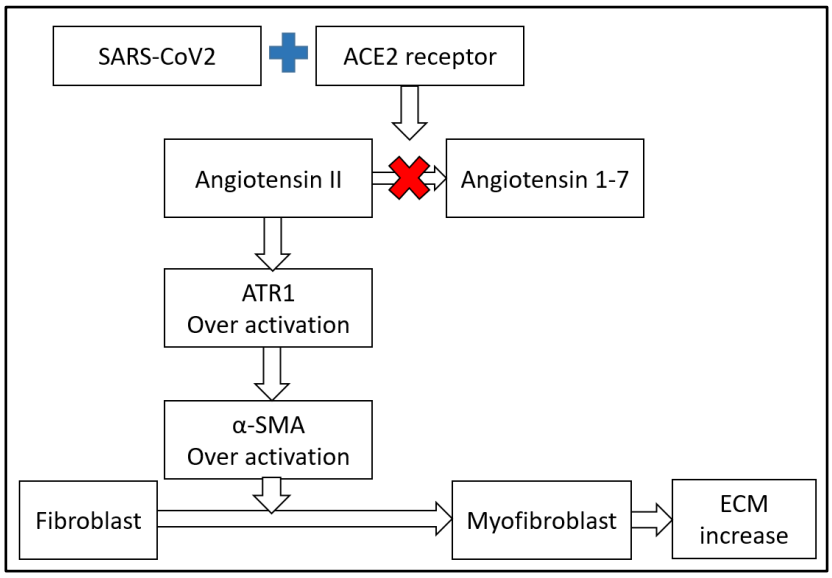

Figure 1. SARS-CoV2-induced fibrosis

In Figure 1, SARS-CoV-2 viruses occupy the ACE-2 receptor, which prevents the conversion of Angiotensin II into Angiotensin (1-7). Therefore, Angiotensin II will occupy the Angiotensin 1 receptor (AT1R). Increased AT1R activation in fibroblast cells will induce the activity of α-Smooth Muscle Actin (α-SMA) in the cytoplasm. This signaling contributes to the differentiation of fibroblasts into myofibroblasts, which play a role in forming ECM.[15,16]

Other mediators, including histamine, bradykinin, and leukotrienes, are released due to the alveolar endothelial injury, which increases endothelial permeability. This will cause fluid to flow into the alveolar and interstitial spaces. Respiratory distress syndrome will appear when the alveolar space is filled with fluid, fibrin, and debris. Ground glass opacity (GGO), consolidation, and septal thickness on lung imaging are characteristics of the presence of airspace exudates, alveolar collapse, and interstitial edema. When traction bronchiectasis is present, pulmonary CT scans may exhibit irregular interlobular septal thickening and reticular patterns. This fibrotic process exhibits symptoms including diffuse alveolar destruction, acute fibrinous, and pneumonia, which are typical of pulmonary fibrosis brought on by SARS-CoV1/2.[11]

Diagnosis of Lung Fibrosis due to COVID-19

Lung fibrosis due to COVID-19 is characterized as a change in the structure of the lung parenchyma by excessive deposition of ECM initiated by COVID-19 infection. In Indonesia, the challenge of diagnosing this condition has been introduced in long COVID-19 patients. The clinical manifestations include coughing, hemoptysis, shortness of breath during activity, fatigue, and chest pain. Physical examination may reveal tachypnea, cyanosis, clubbing fingers, rhonchi, and wheezing on lung auscultation. On investigations such as electrocardiography, the right axis and right ventricular enlargement can be found. Blood gas analysis may reveal hypoxemia or respiratory alkalosis. On spirometry examination, the decreased Total Lung Capacity (TLC)/diffusing capacity of the lungs for carbon monoxide/Residual Volume (RV)/ Force Expiration Volume (FEV)/Force Vital Capacity (FVC) was reported.[17]

The examination of lung function in a patient with lung fibrosis showed a restrictive form of the disorder with hypoxemia and hypocapnia at rest. Several studies suggest that desaturation <88% on the 6-minute walk test (6MWT) predicts mortality in lung fibrosis.[18] Apart from clinical manifestations and several other supportive factors, the diagnosis of lung fibrosis can also be confirmed through imaging examinations. Through chest X-ray, we can find the bibasilar reticular pattern or honeycomb appearance. The thorax CT scan showed GGO, consolidation, and septal thickening. However, the gold standard for lung fibrosis diagnosis is histopathological fibroblastic foci through lung biopsy.[17]

Management of Respiratory Disease Patients' Treatment of Lung Fibrosis due to COVID-19

The treatment approach in lung fibrosis due to COVID-19 is currently studied in phases 3 and 4. However, managing lung fibrosis is generally divided into non-pharmacological and pharmacological therapies. For non-pharmacological therapy, patients with lung fibrosis who experience desaturation during activity or rest can be given long-term oxygen therapy. Respiratory rehabilitation, such as simple breath control exercises, is also recommended in patients with pulmonary fibrosis. A report by the Cochrane Council in 2010 stated that six months of respiratory rehabilitation could improve the outcome of 6MWT and quality of life, especially in mild pulmonary fibrosis. Meanwhile, for patients with pulmonary fibrosis with severe damage and hypoxemia at rest, lung transplantation is recommended, provided that there are no postoperative aggravating conditions and the availability of donors and transplant facilities. Chen, *et al*. reported three cases of patients with severe pulmonary fibrosis due to COVID-19 who underwent lung transplantation. Only two patients were able to survive the procedure.[18]

In pharmacological therapy, since 2003, guidelines for the management of lung fibrosis in the form of glucocorticoids, immunomodulatory, and N-Acetyl cysteine have not been effective in the treatment of lung fibrosis. However, symptomatic therapy is still given, such as antitussive and mucolytic. With the introduction of an era of "anti-fibrotic agents," nintedanib as a triple tyrosine kinase inhibitor that works by inhibiting VEGF, PDGF, and FGF receptors with a dose of 2x150 mg, has the effect of reducing the risk of exacerbations, increasing FVC, and improving quality of life.[18]

Pharmacokinetics of Nintedanib

After oral administration of nintedanib, it is absorbed and reaches its maximal serum concentration (Cmax) within 2-4 hours. Consumption of nintedanib is recommended 30 minutes after meals to increase gastrointestinal tolerance and has been shown to increase absorption by as much as 20%. The distribution of nintedanib is 98% bound to plasma proteins.[19] Nintedanib is largely metabolized by hydrolytic ester cleavage with subsequent glucuronidation and excretion via the liver. After being metabolized, the active drugs released into the plasma are nintedanib (24%), BIBF 1202 (32%), and BIBF 1202 glucuronide (30%). The metabolism of nintedanib is also assisted by the cytochrome P450 (CYP) enzyme, but nintedanib does not inhibit or induce CYP enzymes; therefore, it can be combined with other therapies. The clinical trial study was conducted on eight people who were given oral nintedanib 100 mg and observed the drug elimination pathway. After 120 hours of administration, 93.4% of nintedanib was excreted in feces and biliary excretion. Urinary elimination is very small at 0.65% after 72 hours of administration. In addition, this study also performed IV administration of nintedanib (6 mg). There was no significant difference in the process of elimination of oral or IV administration. Renal elimination is very small in nintedanib, thus the kidney does not have a major role in nintedanib elimination. In analyses performed in phase II and III trials, nintedanib did not cause worsening in patients with mild (Creatinine Clearance Test or CCT 60-90 mL/min) and moderate (CCT 30-60 mL/min) chronic renal conditions. However, this test was not performed in patients with severe renal impairment (CCT <30 mL/min), and therapy in these patients is not recommended.[19]

Patients with moderate to severe hepatic impairment should not be administered nintedanib, while patients with mild hepatic impairment should be closely monitored, and an appropriate dose should be selected. The guidelines for the management of nintedanib in the US and Europe recommend giving nintedanib 100 mg twice daily in patients with IPF and mild hepatic impairment, whereas patients with non-small cell lung carcinoma (NSCLC) and mild hepatic impairment should be closely monitored and an appropriate dose should be selected. Other studies do not recommend the administration of nintedanib in patients with child-pugh B and C. The lethal dose for nintedanib based on clinical trials in experimental animals was >2000 mg/Kg on oral administration and >40mg/Kg on IV administration. Pregnancy is included in category D because, in experimental animals, it influences the embryogenic process. [19] The most common side effects of nintedanib are gastrointestinal disorders such as diarrhea, followed by nausea and constipation. In 670 subjects who received nintedanib 2x150 mg for 52 weeks, there was an increase in liver enzymes in 351 subjects, but none of these subjects experienced an increase of >2 upper limits normal for Aspartate Transaminase (AST) and Alanine

Transaminase (ALT), or an increase in total bilirubin less than 1x upper limit normal.[20]

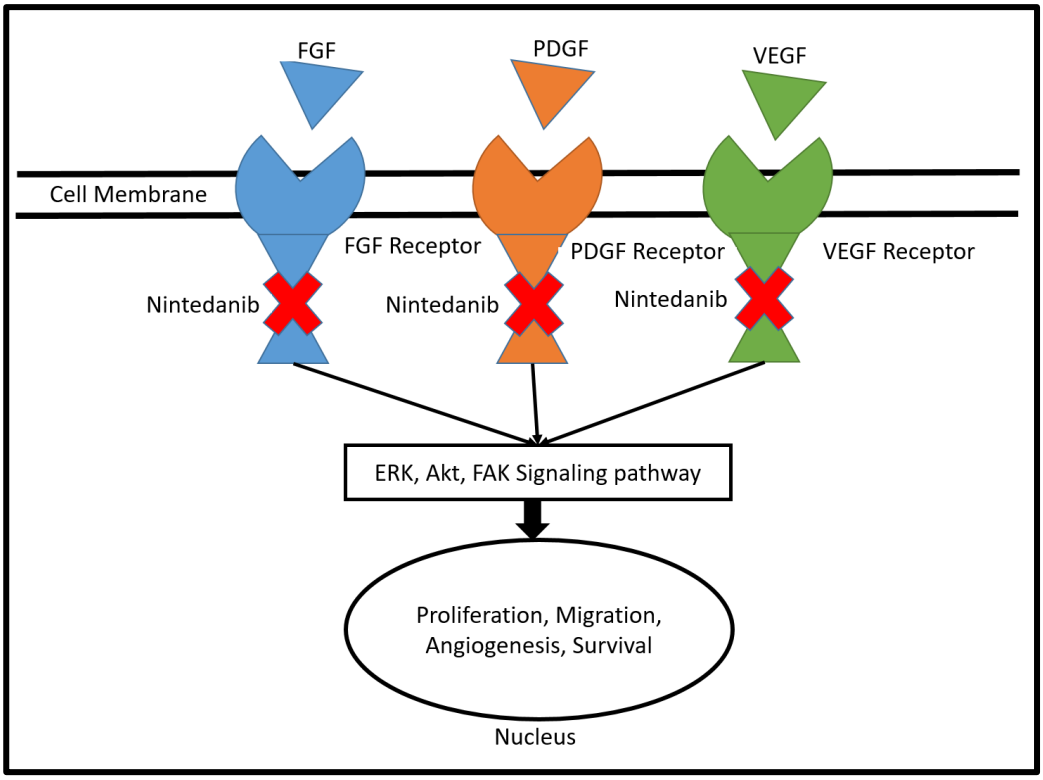

Figure 2. Nintedanib schematic mechanism of action

Mechanism of Action of Nintedanib in COVID-19-Related Lung Fibrosis

Nintedanib is an oral drug that functions as a tyrosine kinase molecule inhibitor and is currently used for managing IPF and patients with advanced adenocarcinoma. It inhibits the receptor kinase activity of VEGF, PDGF, and FGF. It will bind to the ATP receptor pocket of FGF, PDGF, and VEGF, causing blockade of receptor autophosphorylation and signal inhibition to the cell nucleus by preventing phosphorylation of extracellular signal-regulated kinase (ERK) pathways, protein kinase B (PKB or Akt), and focal adhesion kinase (FAK). Those pathways will interfere with the DNA transcription in the nucleus, thus preventing the proliferation, migration, angiogenesis, and survival of fibrotic cells (Figure 2).[21]

In vitro preclinical testing on nintedanib showed concentration-dependent kinase inhibition. The targeted kinases that can be inhibited are VEGF types 1-3, FGF types 1-3, and PDGF. In vivo study shows a decrease in collagen in lung tissue. Nintedanib also has an anti-inflammatory effect with an unknown mechanism. This is evidenced by decreased IL-1, chemokines, and lymphocytes in bronchoalveolar lavage (BAL) fluid analysis.[5,7]

Clinical Studies of Nintedanib Related to COVID-19

Chakrabortty, *et al*. reported a case study on a 40-year-old male COVID-19 survivor with critical symptoms of ARDS and comorbid type 2 diabetes mellitus receiving treatment in the ICU for 20 days. After being discharged from the hospital, the patient was outpatient for 50 days with persistent complaints, namely a continuous dry cough and shortness of breath during activity. Data during previous treatment showed peripheral and basal GGO of both lungs and consolidation with lung parenchymal involvement of about 45–55%. Spirometry examination showed a restrictive type with decreased DLCO. 6MWT showed oxygen desaturation. Patients with shortness of breath on activity and 93% oxygen saturation showed no significant changes from imaging studies. The patient was given nintedanib 2x150mg. After 15 days, the patient experienced improvement, such as shortness of breath and an oxygen saturation level of 98%. CT scan of the thorax showed an improvement, the same as spirometry results with FVC from 35% to 63.5%. DLCO increased from 3.8% to 45%, TLC increased from 5.4% to 61.7%, and 6MWT of 1300 steps and 98% SpO_2.[22]

Ogata, *et al*. reported a case study on a 78-year-old woman with a history of COVID-19 critical symptoms, comorbid hypertension, post-ICU treatment with a ventilator for four weeks, and a CT scan of the thorax in the form of fibrosis of both lungs. During the 28 days post-ICU, the patient experienced a drastic decrease in lung function, both from the CT scan of the thorax and spirometry. The patient then underwent respiratory rehabilitation and was given nintedanib 150mg BID. The patient experienced side effects of nintedanib, namely an increase in liver function. The dose was reduced to 2x100mg, and the liver function improved. The patient experienced significant improvement after three months of nintedanib administration. The patient could walk independently with nasal cannula oxygen supplementation at 4 lpm. CT scan of the thorax revealed progressively diminishing lung fibrosis in two months.[23]

Umemura, *et al*. conducted a clinical trial of administering nintedanib to ARDS patients due to COVID-19 who were on a ventilator. It was found that the group who was given nintedanib had a 23% lower risk of mortality during 28 days of monitoring and a higher P/F ratio in nintedanib group than the control group.[24] Crestani, *et al*. are recruiting a clinical trial of nintedanib for the treatment of SARS-CoV2-induced pulmonary fibrosis (NINTECOR), which is estimated to finish in 2024 and requires 250 COVID-19-related lung fibrosis survivors to interfere with nintedanib 150mg BID for 12 months.[25] Marwah, *et al*. published a case series of four patients with moderate to severe COVID-19 symptoms and lung fibrosis as revealed by a CT scan. The decision to take nintedanib 150mg BID for four weeks was made. All patients were well-tolerated and showed a significant reduction in lung fibrosis.[26]

George, *et al*. reported a case study on a 67-year-old woman who had a critical case of COVID-19 and developed lung fibrosis. The patient was given nintedanib 150mg BID for three months, resulting in improved lung function using a serial 6MWT, spirometry, and chest CT scan.[27] Bussolari, *et al*. reported a case series of three patients aged between 42 and 52 years old with severe COVID-19 and obesity who started nintedanib 150mg BID due to the difficulty of obtaining lung function and restoration. Soon after the beginning of the treatment, systemic inflammation and respiratory function rapidly improved. Serial chest CT scans confirmed the progressive lung amelioration, also reflected by functional tests during follow-up.[28]

SUMMARY

Nintedanib is a tyrosine kinase inhibitor and is currently one of the drugs used in treating pulmonary fibrosis. It inhibits the receptor kinase activity of VEGF, PDGF, and FGF, inhibiting the fibroblasts' proliferation, migration, and transformation into myofibroblasts in lung fibrogenesis. It has been reported in some cases of COVID-19-related lung fibrosis and has shown a significant effect on reducing the appearance of lung fibrosis and improving lung function and quality of life in patients. There are no reports of harmful interactions with nintedanib with other drugs. Nintedanib has tolerable side effects such as diarrhea and mild elevation of liver enzymes. According to several clinical studies, nintedanib treatment in both acute and long-term phases of COVID-19 patients has shown beneficial effects on lung fibrosis reduction and potentially improved quality of life.

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Conflict of Interest
The author declared there is no conflict of interest.

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Author's Contributions
Conceiving, analyzing, reviewing, and revising the manuscript: ZA. Writing manuscript: AF. Literature searching and analyzing: LA and RP. Reviewing manuscript: S, AR, TS. All authors contributed and approved the final version.

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