Original Article

Management of Pulmonary Fibrosis from COVID-19 Pneumonia with Nintedanib

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Abstract

OBJECTIVES: To propose the benefit of antifibrotic agent, nintedanib, in the treatment of lung fibrosis from SARS-CoV-2 Coronavirus 2019 (COVID-19) pneumonia, based on experience at Bangkok Hospital Headquarters, Bangkok, Thailand.

MATERIALS AND METHODS: Data from patients who developed lung fibrosis post COVID-19 pneumonia during 2020-2022 at our institute, all developed severe pneumonia, was analyzed, including clinical signs and symptoms, imaging findings, O2 saturation: at room air and during 6 minutes' walk, and response to treatment.

RESULTS: Among 10 patients with COVID-19 lung fibrosis who received steroids, remdesivir and nintedanib; 2 patients (20%) expired, 7 patients (70%) were back to normal within 3 months, and
1 patient (10%) was able to walk with oxygen 2 liter per minute (LPM) after 7 months.

CONCLUSION: An antifibrotic agent, such as nintedanib, could improve lung fibrosis from COVID-19 pneumonia.

Keywords: lung fibrosis, COVID-19 infection, long COVID, antifibrotic agent, nintedanib

In 2020-2022, after the outbreak of coronavirus disease in 2019 (COVID-19) which became a global endemic catastrophe, about one fifth of patients developed long COVID in terms of lung involvement, cardiac problems, neurological disorders or immunological syndromes. The most severe form of lung disorders are those where lung fibrosis develops.

Lung fibrosis is one of the sequelae of COVID-19 infection, and permanent pulmonary architectural distortion and irreversible lung dysfunction can occur due to pulmonary fibrosis.[1] The major risk factors for severe COVID-19 are increasing age, male and comorbidities such as hypertension, diabetes and these severe infections are responsible for lung fibrosis. SARS-CoV-2 attacks the tissue covering the lung alveoli and causes profound fibrosis in the form of excess collagen tissue deposited in the lung.[2] The role of antifibrotic agents is still poorly defined. Here we described the benefits of antifibrotic agents in patients with ongoing SARS-CoV-2 virus infection to delay the worsening of the clinical conditions.

Material and methods

We drew on 10 cases of COVID-19 lung fibrosis between 2020-2022, all developed severe pneumonia, received treatment with high flow oxygen or mechanical ventilation, steroid, remdesivir and nintendanib.

Results

The patients were 6 females and 4 males; ages ranged from 45 to 93 years old with an average age of 64.6 ± 7.2 years. There were 7 patients with underlying diseases: such as diabetes, chronic obstructive airway disease, heart disease and hyperlipidemia. (Table1)

Two patients expired from severe pneumonia in the 4th week of treatment; five patients improved with lung functions were back to normal in 3 months, three patients needed tracheostomy due to prolonged intubation, all could be extubated; 2 of them were working normally within 3 months. The last patient, referred from another medical institution in the middle east, presented with post COVID-19 lung fibrosis for 4 months, at first he could not even walk due to severe hypoxia, then nintedanib was administered for 6 months, from which point he could walk with portable oxygen 2 liters per minute, his 6 minutes' walk test revealed oxygen saturation of 94% and his computed tomography of the chest revealed improvement of lung fibrosis, (Figure 1) with sequelae of traction bronchiectasis (Figure 2).

Table 1 outlines clinical data among 10 patients who developed covid pneumonia with lung fibrosis complications who received nintedanib

Table 1: Baseline Clinical and demographic characteristics of the subjects (n = 10)

No	Age (Years)	Gender M = Male F = Female	Underlying disease	Duration of nintedanib (Months)	Outcome
1	93	F	Heart diseases	1	Expired
2	90	F	COPD	1	Expired
3	87	F	DM	3	Survived
4	72	F	Heart diseases	3	Survived
5	65	F	Hyperlipidemia	2	Survived
6	63	F	Obesity	3	Survived
7	92	M	Heart diseases	2	Survived
8	60	M	No	3	Survived
9	58	M	No	3	Survived
10	45	M	No	7	Improvement of oxygen saturation after 7 months of nintedanib

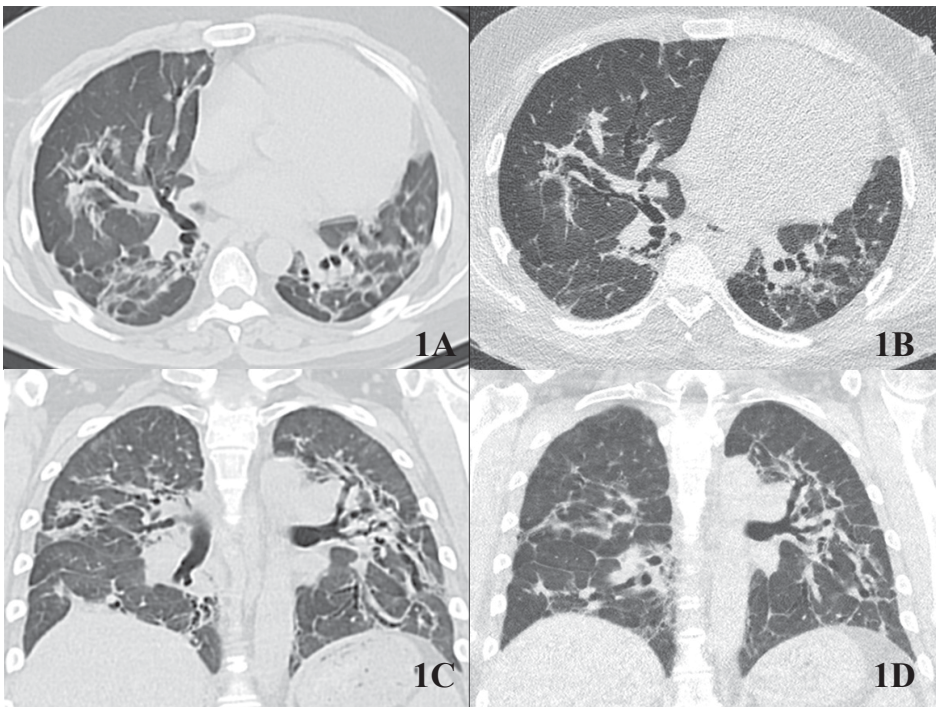

Figure 1: The axial and coronal CT views of a COVID-19 patient taken at 10-month interval, showing a multifocal thin band-like peribronchial opacity in both lungs with mild traction bronchiectasis at the initial (1A, 1C) and at the follow-up (1B, 1D) with much decreased thin band-like peribronchial opacity, but increased in degree of traction bronchiectasis diffusely.

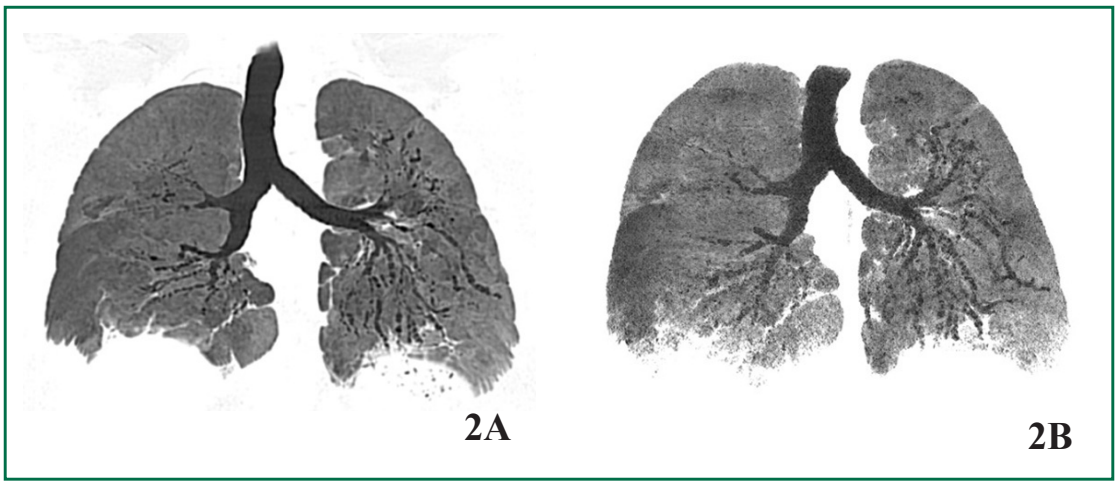

Figure 2: The minimum intensity projection (MinIP) images show interval increased degree of diffuse traction bronchiectasis in the 10-month interval on the initial (2A) and follow-up (2B) studies.

Discussion

Diffuse lung damage during COVID-19 infectionm associated with acute respiratory distress syndrome (ARDS), is characterized by acute phase of inflammation, edema and hyaline formation, followed by an organizing phase of fibrin in the alveolar septa. The next stage is the fibrotic stage which can either resolve completely or progress to fibrosis.[3]

The duration of the acute disease seemed to be a major factor of fibrotic lung (<1 week =4%,between 1 and 3 weeks =24%, and >3 weeks = 61%).[3]

Interventional study by administration of nintenadib in one study in 30 patients who required mechanical ventilation, [4] comparing 30 intubated patients with COVID-19 pneumonia without nintedanib. There was no significant difference in 28-day mortality between the groups (23.3% vs 20%, $p = 0.834$). The mortality rate was 20% in our group which was similar.

Lengths of mechanical ventilation were significantly shorter in the nintedanib group ($p = 0.04$). Computed tomography showed the percentage of high attenuation areas were significantly lower in the nintedanib group at liberation from mechanical ventilation (38.7% vs 25.7%, $p = 0.027$). The authors concluded that nintedanib may offer potential benefits for minimizing lung injury in COVID-19.

For longer duration of treatment, Ogata[5] reported on a case of severe pulmonary fibrosis from COVID-19, nintedanib was administered with steroid, the patient could be extubated, 3 months later, she could walk with a walking aid using oxygen at 4 LPM.

Another case report by Vitug[6], included administration of nintedanib for 3 months in one case of COVID-19 induced lung fibrosis, resulting in lung function improvement by 6-minute walk test, spirometry, pre and post treated high-resolution computed tomography (HRCT) of the lung.

In 2022, Singh[7] conducted a prospective study in 56 patients of COVID-19 pneumonia; 19 patients received steroid only as a control group,16 patients received steroid with pirfenidone and 21 cases received steroid and nintedanib. The primary end point was the improvement of CT severity score (CTSS). The authors found that there was significant improvement in CTSS in the group receiving nintedanib compared to the group receiving pirfenidone at 12 weeks with a $p < 0.01$

One of our group received nintedanib and responded well for 7 months which was the longest period so far reported.

Conclusion

Nintedanib, an antifibrotic agent, may play role in improving lung fibrosis from COVID-19 pneumonia.

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