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Use of Nintedanib and its Outcome among Post-COVID Pulmonary Fibrosis Patients Residing at High Altitudes: A Case Series

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ABSTRACT

Introduction: The purpose of this study was to determine the effect of nintedanib among critically ill COVID-19 patients and to assess its effect on their clinical status and radiological resolution from post-COVID pulmonary fibrosis. Antifibrotic drugs, such as Nintedanib, have emerged as an early treatment option for prevention and during post-COVID-19 pulmonary fibrosis which has been seen as early as 3 Weeks.

Case Presentation: A total of 4 critically ill COVID-19 patients confirmed by reverse transcriptase polymerase chain reaction were prescribed Nintedanib 4 weeks after intensive care unit (ICU) admission, at the dose of Idiopathic Pulmonary fibrosis (IPF). The dose was started from 100 mg BD for 10 days and then increased to 150 mg BD as tolerated by the patient. One patient lost follow-up on discharge, and another patient's drug had to be stopped in between due to adverse effects. So, two patients regularly followed for 1, 3, and 6 months after discharge and even after the stoppage of drugs. Over the period they showed drastic improvement in oxygen requirements, resting oxygen saturation, and symptoms such as cough and dyspnea. Serial high-resolution computed tomography (HRCT) chest scans and lung function tests were performed during follow-up to confirm progressive lung enhancement.

Conclusion: The use of nintedanib seems to have minimized the lung injury induced by COVID-19 after continuous follow-up for a period of 9 months both clinically and radiologically with improvement in lung function.

Key Words: Coronavirus disease; Pulmonary fibrosis; Severe acute respiratory syndrome

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which was declared a global pandemic on March 11, 2020.[1] It has resulted in 7 billion infections (772,166,517 confirmed cases) and nearly 6 million deaths globally as reported to the World

Health Organization (WHO) by 18 November 2023. In Nepal, from 3 January 2020 to 28 March 2022, there have been 978,347 confirmed cases of COVID-19 with 11,951 deaths. [2] Risk factors and existing comorbid conditions such as advanced age with limited lung function, diabetes, hypertension, cardiovascular diseases, and obesity play a pivotal role in severe COVID-19. [3] COVID-19 has been found to cause similar respiratory symptoms as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronavirus, suggesting that SARS-CoV-2 infection may also cause fibrotic consequences. [4] SARS-CoV-2 attacks the tissue by binding to the angiotensin-converting enzyme 2 (ACE2) receptor and affects lung alveoli causing excess collagen tissue deposition which may result in profound fibrosis of lung tissue. [5] Post-COVID pulmonary fibrosis (PCPF) has been recognized as a potentially worrying sequel among survivors as they develop permanent pulmonary architectural distortion and irreversible pulmonary dysfunction. [6] Although the role of antifibrotic therapy in pulmonary fibrosis due to SARS-CoV-2 infection has not been proven, drugs such as pirfenidone and nintedanib, have emerged as early treatment options for preventing pulmonary fibrosis among COVID-19 patients which can present as early as 3 weeks post-acute respiratory distress syndrome (ARDS). [7] Nintedanib, an intracellular inhibitor of tyrosine kinase acts by interfering with the process of active fibrosis such as the proliferation, migration, and differentiation of fibroblasts. [8]

The purpose of this study was to determine the effect of nintedanib among critically ill COVID-19 patients and to assess its effect on their clinical status and radiological resolution from PCPF.

CASE PRESENTATION

A total of 4 critically ill COVID-19 patients confirmed by reverse transcriptase polymerase chain reaction were prescribed Nintedanib 4 weeks after intensive care unit (ICU) admission in Karnali Academy of Health Sciences, Jumla, at the dose of Idiopathic Pulmonary fibrosis (IPF).

On admission clinical findings **(Table 1)**, vitals **(Table 2)**, ABG **(Figure 1)**, and blood parameters were measured and repeated as per clinical requirements. One patient lost follow-up on discharge, and another patient's drug had to be stopped in between due to adverse effects. Thus, only two patients who regularly visited our center for periods of 1, 3, and 6 months after discharge and even after the stoppage of drugs have been summarized here.

Case 1: 36yr/M was admitted to the High Dependency Unit (HDU) and started on high flow moist O2 using the non-rebreathing mask (NRM), along with intravenous (iv) injection of 6 mg dexamethasone once daily, twice daily (BD) subcutaneous injection of 60 mg enoxaparin and Meter Dose inhaler (MDI) Budesonide 400ug BD. His bedside chest X-ray (CXR) revealed bilateral moderate peripheral haziness. On day 2, the patient's oxygen requirement increased, his saturation dropped to 50%, and was transferred to the ICU where he was kept in non-invasive ventilation (NIV) using a mechanical ventilator (MV) with a 100% fraction of inspired oxygen (FiO2) and intermittent awake proning was performed. The patient was given an injection of 200 mg Remdesivir, followed by 100 mg administered intravenously for 5 days during the ICU stay. He was on NIV intermittently until day 23, followed by a gradual decrease in FiO2, and shifted to the medicine ward with non-rebreathing mask support. On day 28, the patient had Chest high-resolution computed tomography (HRCT) revealing multiple confluent areas of consolidation and ground-glass opacities (GGO) with poster dorsal predominance and peribronchial distribution (25% area). The patient was counselled and started on nintedanib initially at 100mg, which was well tolerated by the patient, and over the period drastic improvement in oxygen requirement, resting oxygen saturation, and symptoms such as cough and dyspnea were seen. The patient was discharged from the hospital after a total of 45 days of hospital stay on domiciliary oxygen

2l/min, with a tapering dose of steroids, and nintedanib 150mg BD for the period of 3 months. He visited the Outpatient (OPD) medicine department a total of 4 times over 6 months with follow-up HRCT and spirometry done and vitals over time **(Table 3)** improved with no oxygen requirement and HRCT chest showed no GGO.

Case 2: 56/M ex-smoker, alcohol consumer presented to our center and was admitted to the ICU under NIV using MV with FiO2 100% and intermittent awake proning. The patient was given all the medications as in case 1 remdesivir, enoxaparin, and a high-dose steroid (Inj dexamethasone 6mg BD) with MDI budesonide. He stayed for 20 days in the ICU and then shifted to the medical ward under oxygen at 15 L/min using NRM with intermittent incentive spirometry exercise and chest physiotherapy. On day 25, HRCT was performed which showed areas of GGO with, a crazy-paving pattern (>25%) with areas of fibrosis. The patient was then started on nintedanib 100mg BD followed by 150mg BD for 6 months. The patient was discharged from the hospital for 40 days under domiciliary oxygen 3-4L/min and nintedanib which improved his symptoms. Follow-up vitals **(Table 3)** and Spirometry **(Figure 3)** with HRCT Chest findings **(Figure 3)** are shown. Although, the patient's symptoms improved with SpO2 88% in room air his HRCT chest shows multiple areas of fibrosis predominant in the bilateral upper lobe with traction bronchiectasis and GGO in a few areas. He took nintedanib 150mg BD for a period of 6 months and an MDI with domiciliary oxygen for a period of 1 year.

Table 1: Clinical Presentation of Cases

Features	**36/ M**	**56/M**	**56/M**	**63/M**
Fever	5D	5 D	5D	12 D
Cough		3D	5D	7D
Dyspnea		3D	4D	7D
Abdominal pain	3D			
History			Seizure disorder	
Smoker		Ex-smoker	Past Smoker	Ex-smoker
Alcohol		Alcohol Consumer		

Table 2: Presentation during admission

VITALS	**CASE1**	**CASE2**	**CASE3**	**CASE 4**
SPO2	56%	36%	68%	78%
BP	110/80	130/80	80/60	110/70
HR	130	126	110	110
Temp	101.6	100.6	97.9	102
RR	44	66	35	44

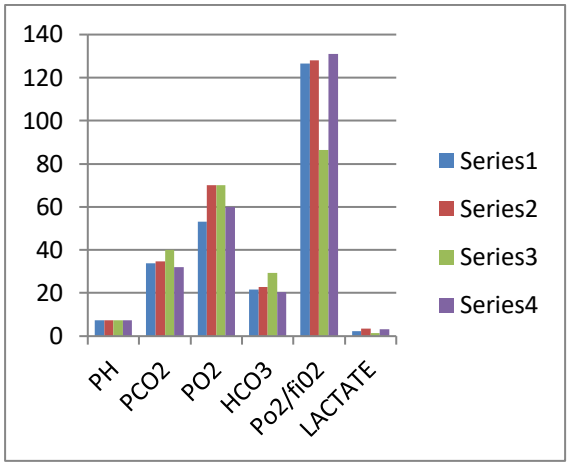


Figure 1: ABG findings at admission

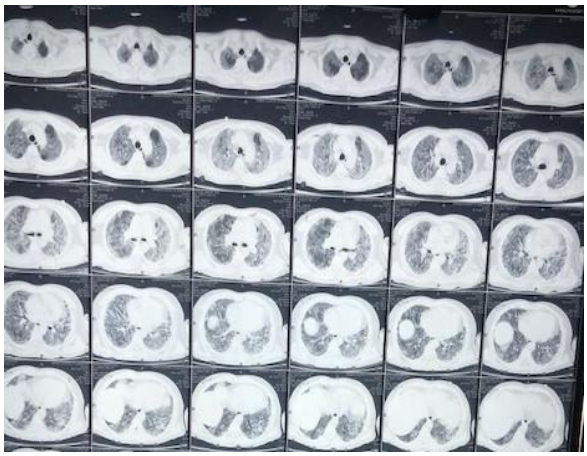
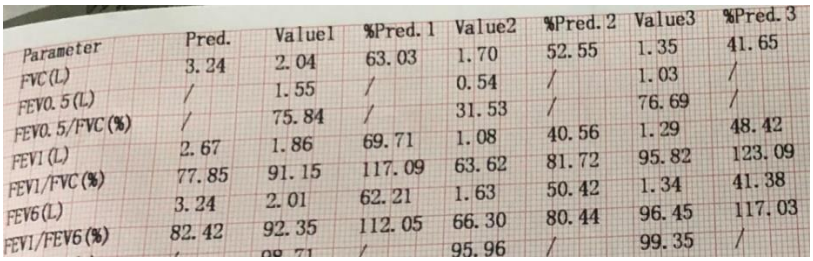


Figure 2: HRCT Chest Findings (Case 2)



Parameter	Pred.	Value1	%Pred. 1	Value2	%Pred. 2	Value3	%Pred. 3
FVC (L)	3. 24	2. 04	63. 03	1. 70	52. 55	1. 35	41. 65
FEV0. 5 (L)	/	1. 55	/	0. 54	/	1. 03	/
FEV0. 5/FVC (%)	/	75. 84	/	31. 53	/	76. 69	/
FEV1 (L)	2. 67	1. 86	69. 71	1. 08	40. 56	1. 29	48. 42
FEV1/FVC (%)	77. 85	91. 15	117. 09	63. 62	81. 72	95. 82	123. 09
FEV6 (L)	3. 24	2. 01	62. 21	1. 63	50. 42	1. 34	41. 38
FEV1/FEV6 (%)	82. 42	92. 35	112. 05	66. 30	80. 44	96. 45	117. 03
				95. 96	/	99. 35	/

Figure 3: Spirometry Findings (Post Nintedanib Use) Case 2.

Table 3: Presentation during follow-up

VITALS	**36/M**		**56/M**	
	3mth	**6mth**	**3mth**	**6mth**
SPO2 at Rest	86%	92%	82 %	90%
BP mmhg	110/80	110/80	130/80	110/80
HR/min	90	72	88	76
Temp F	97.8 F	98.2F	98.9F	97.8F
RR/min	22	18	20	16

DISCUSSION

COVID-19 has a range of clinical presentations from mild (40%) to severe illness (15%) requiring oxygen and 5% results in a critical form causing respiratory failure, ARDS, sepsis and septic shock, thromboembolism, and multiorgan failure. [6] In critical cases, patients require MV or NIV due to Acute respiratory failure (ARF) which has resulted in concerns regarding pulmonary sequelae mostly PF(Pulmonary Fibrosis). [9] There have been many postulates resulting in lung injury in COVID-19, with both virus-direct injury and immune-mediated mechanisms besides these, other factors could also play roles in causing severe lung injury, increased risk of mortality, or PF among survivors. [10] PCPF mostly occurs among patients with advanced age, the extent of comorbidity, severity of disease, length of ICU admission, and need for mechanical ventilation. [11] In our study, three patients were elderly, ex-smokers with severe symptoms on presentation, which could be a cause for their severe illness with PCPF whereas

one patient was young with no comorbid conditions. Rai et al, also stated that the development of lung fibrosis in COVID-19 might be due to advanced age, which is similar to MERS and SARS-CoV-1.[12] Fibrotic abnormalities have been detected as early as 3 weeks after the onset of symptoms in all mild, moderate, and severe conditions. Thus, PCPF can present at any time from initial hospitalization to long-term follow-up. A similar finding was suggested by Umemura et al, who stated that in the ARDS course, PF could develop at any time. [13,8]

HRCT chest plays an important role in diagnosing COVID-19 and findings vary according to symptom onset which has been divided into 4 stages (a) early stage (0–5 days onset) presenting with normal CT (b) progressive stage (after 5–8 days) increased GGO and crazy-paving appearance (c) peak stage (after 9–13 days) progressive consolidation and (d) late stage (after 14 days) characterized by a gradual decrease in consolidation and GGO, with signs of fibrosis (including parenchymal bands, architectural distortion, irregular interfaces, reticulation, and traction bronchiectasis). [14] The CT severity score (CT-SS) developed for COVID-19 also plays an important role in the prediction of disease progression. Ali et al showed that the group with a CT-SS of 18–25 had a higher incidence of PCPF. [6] Similarly Zhou F et al. stated that increased disease severity has reliable evidence of lung tissue destruction and correlates well with mortality risk. [15] In our study, the CT-SS score was severe (18-25) among all four patients.

To date, there has been no definitive therapeutic intervention for preventing or managing PCPF. Many have proposed that early use of antiviral, anti-inflammatory, and antifibrotic drugs might reduce the likelihood of the development of lung fibrosis. [7] Although the role of antifibrotic drugs in PCPF has not yet been proven, it is still believed that they are useful in patients with ILD (both IPF and other fibrotic ILDs), as they lessen pulmonary damage, thus reducing morbidity and mortality rates. Thus, antifibrotic drugs, such as pirfenidone and nintedanib, can be used in the acute phase of COVID-19 pneumonia as they have anti-inflammatory effects and have been shown to reduce the decline in lung function by approximately 50%.[6,14]

In our study, nintedanib was used in the dose of IPF for 3 months with regular follow-up, which showed a significant reduction in oxygen requirement, improvement in symptoms such as dyspnea on movement, and shortened hospital stay with pre-and post-treatment HRCT chest improvement. Throughout the course of treatment, we watched for side effects such as hepatotoxicity which in our patients were within normal levels.

Nintedanib is a tyrosine kinase inhibitor that affects vascular endothelial growth factor, platelet-derived growth factor, and fibroblast growth factor which are increased among COVID-19 patients. In addition, it also decreases the expression of IL-1 and IL-6, which play a central role in the COVID-19 cytokine storm leading to fibrogenesis in the lung. [16]

CONCLUSION

IPF and COVID-19 lung fibrosis might have similar mechanisms in inducing lung fibrosis; hence antifibrotic targeted therapy such as nintedanib can be used as an adjunct treatment for individuals who develop pulmonary fibrosis due to COVID-19. It could improve pulmonary function and reduce the rate of functional decline of the lungs; however, there is still no certainty on its effect on the reversal of pulmonary fibrosis. Hence, a randomized controlled trial should be performed to determine the effectiveness and safety of nintedanib and its impact on patients with post-COVID pulmonary fibrosis, especially among vulnerable individuals.

REFERENCES

1. Coronavirus disease (COVID-19).

2. WHO Coronavirus (COVID-19) Dashboard.
3. Mohammadi A, Balan I, Yadav S, Matos FW, Kharawala A, Gaddam, et al. Post-COVID-19 Pulmonary Fibrosis. Cureus. 2022;14(3): e22770.
4. Li Xiaohe, Shen Chenguang, Wang Lifei, Majumder Sumit, Zhang Die, Deen M. Jamal et al. Pulmonary fibrosis and its related factors in discharged patients with new coronavirus pneumonia: a cohort study. Respir Res. 2021;23:203.
5. Chakrabortty R, Rahman S, Jahan R, Dip AH, Rahman MM. Nintedanib in the management of pulmonary fibrosis after COVID-19: a case report. BIRDEM Med J. 2021;11(2):148-52.
6. Ali Mohamed MR, Ghonimy Ibrahim B Mai. Post-COVID-19 pneumonia lung fibrosis: a worrisome sequela in surviving patients. Egyptian Journal of Radiology and Nuclear Medicine 2021;52:101.
7. Rai KD, Sharma P, Kumar R. Post covid 19 pulmonary fibrosis. Is it real threat? Indian Journal of Tuberculosis 2021;68:330-333.
8. Umemura Y, Mitsuyama Y, Minami K, Nishida T, Watanabe A, Okada N, et al. Efficacy and safety of nintedanib for pulmonary fibrosis in severe pneumonia induced by COVID-19: An interventional study. International Journal of Infectious Diseases 2021;108: 454–460.
9. Ambardar SR, Hightower SL, Huprikar NA, Chung KK, Singhal A, Collen JF. Post-COVID-19 Pulmonary Fibrosis: Novel Sequelae of the Current Pandemic. J.Clin. Med 2021;10:2452.
10. Mamun SM Abdullah Al, Jahan R, Islam Quazi Tarikul, Nazrin T, Shajalal K. Rationale of Using Common Antifibrotic Therapy in Post COVID Fibrosis. J MEDICINE 2021;22:46-50.
11. Earl N, Schoeneberg D, Davidson PD. BMJ Case Rep 2021;14:e244472.
12. Rai DK, Kumar S, Sahay N. Post-COVID-19 pulmonary fibrosis: A case series and review of literature. J Family Med Prim Care 2021;10: 2028-2031.
13. Karmakar S, Sharma P, Harishkumar A, Rai D K. Post-COVID-19 Pulmonary Fibrosis: Report of Two Cases. EMJ Respir. 2021.
14. Kwee Thomas C and Kwee Robert M. Chest CT in COVID-19: What the Radiologist Needs to Know. RadioGraphics 2020;40(7):1848–1865.
15. Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395(10229):1054–1062.
16. Ogata H, Nakagawa T, Sakoda S, Ishimatsu A, Taguchi K, Kadowaki M., et al. Nintedanib treatment for pulmonary fibrosis after coronavirus disease 2019. Respirology Case Reports 2021;9(5):e00744.