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RESEARCH ARTICLE

THE USE OF NINTEDANIB IN THE TREATMENT OF POST-COVID-19 FIBROSIS

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Abstract

Pulmonary fibrosis is becoming a recognized complication of coronavirus disease 2019 (COVID-19). We report 2 cases of 2 patients aged 40 and 61 with pulmonary fibrosis due to COVID-19. The clinical examination showed that the 2 patients were dyspneic with a weak oxygen saturation and that there was bilateral crackles of the two pulmonary fields. High-resolution computed tomography showed bilateral multifocal ground glass opacities, subpleural fibrotic bands (between 25-50% and 75% parenchymal involvement). We prescribed them an anti-fibrosant, nintedanib, and there was a significant clinical and radiological improvement after 15 days of treatment. Nintedanib may have a new therapeutic role in the prevention of fibrosis associated with COVID-19.

Introduction:-

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus causing the most massive pandemic of the decade. Much research is underway to understand the pathophysiology, clinical course and management of COVID-19 infection, with particular emphasis on treatment modalities.

One of the complications of COVID-19 pneumonia is pulmonary fibrosis [1]. Although there are currently no clinical data on the frequency and mechanism of post-COVID-19 pulmonary fibrosis, it is estimated to affect approximately one-third of patients hospitalized with SARS-COV-2 [1, 2]. This indicates that a combined prevalence in admitted and out-of-hospital patients may be even higher. Likewise, the management of pulmonary fibrosis after COVID-19 infection remains largely unexplored due to a lack of clinical trials. A potential role for antifibrinolytic therapies is suggested based on anecdotal evidence and a proposed similarity in the mechanism of post-COVID-19 pulmonary fibrosis to idiopathic pulmonary fibrosis (IPF) [1–3].

Progressive, fibrotic, irreversible interstitial lung disease is defined as decreased lung function, increased extent of fibrosis by computed tomography (CT), worsening of symptoms and quality of life, and early mortality. [4–5]

We present 2 cases of COVID-19 pneumonia successfully treated with nintedanib, who developed pulmonary fibrosis.

Clinical case :

Case 1:

This is a 61-year-old patient, having thyroidectomy under levothyrox 125µg / day as ATCDs and followed for type 2 diabetes under Repaglinide + Janumet for 20 years, admitted to intensive care for multidisciplinary management of her covid-19 pneumonia superinected, with compatible pulmonary involvement estimated to be 75%.

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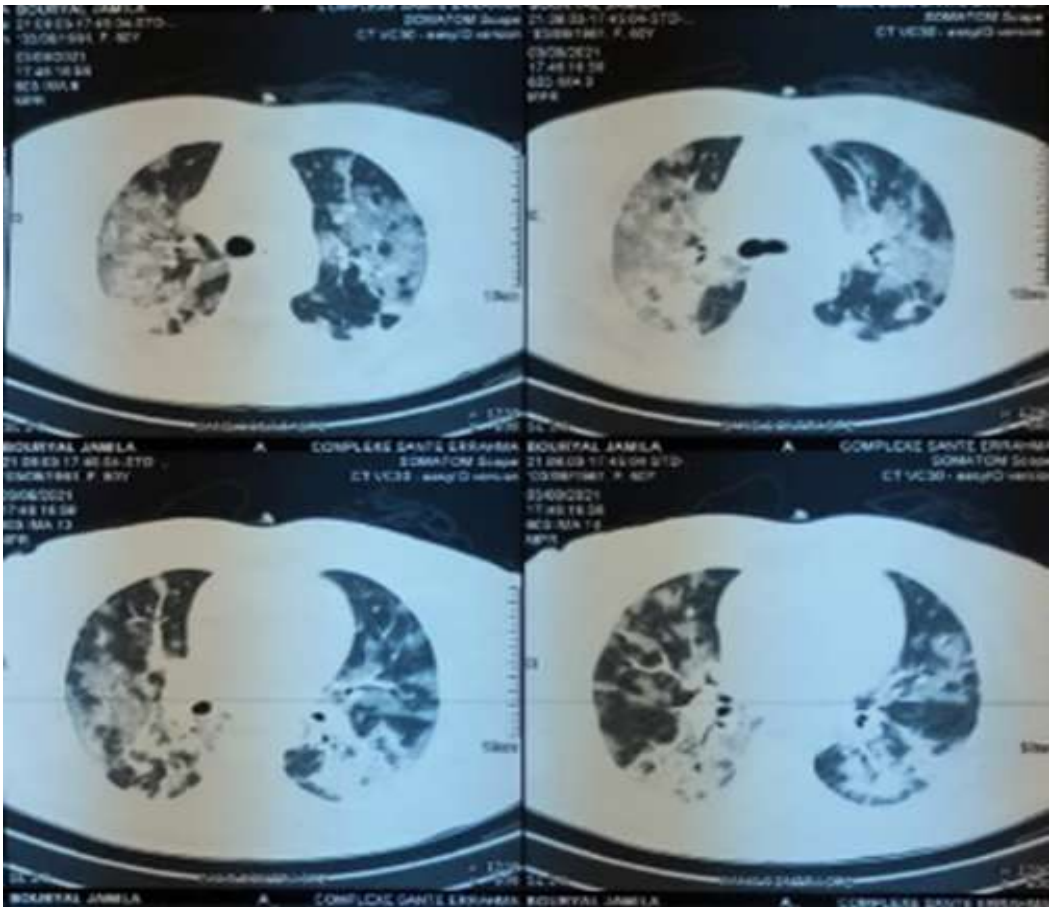

Figure 1:- Chest CT on admission.

Initially, the patient was on continuous non-invasive ventilation for 4 days, then she was put on a high-concentration mask with progressive oxygen reduction. The patient received antibiotic therapy based on imepenem + Levofloxacin + voriconazole, methylprednisolone with a dose of 80 mg / d, LMWH with a curative dose and aspirin 100 mg / d. The evolution was marked by a clinical-biological improvement after which the patient was declared discharged under a 3l / min glasses.

The patient was hospitalized for the second time due to oxygen dependence and increased requirements up to 12L / min and the recurrence of dyspnea on exertion and the appearance of fibrosis lesions on the chest CT scan. Oral treatment with nintedanib at a dose of 300 mg / day in 2 doses was started, with armed biological monitoring every other day, without alteration of hepatic enzymes or renal function, haematological disturbances or other undesirable effects.

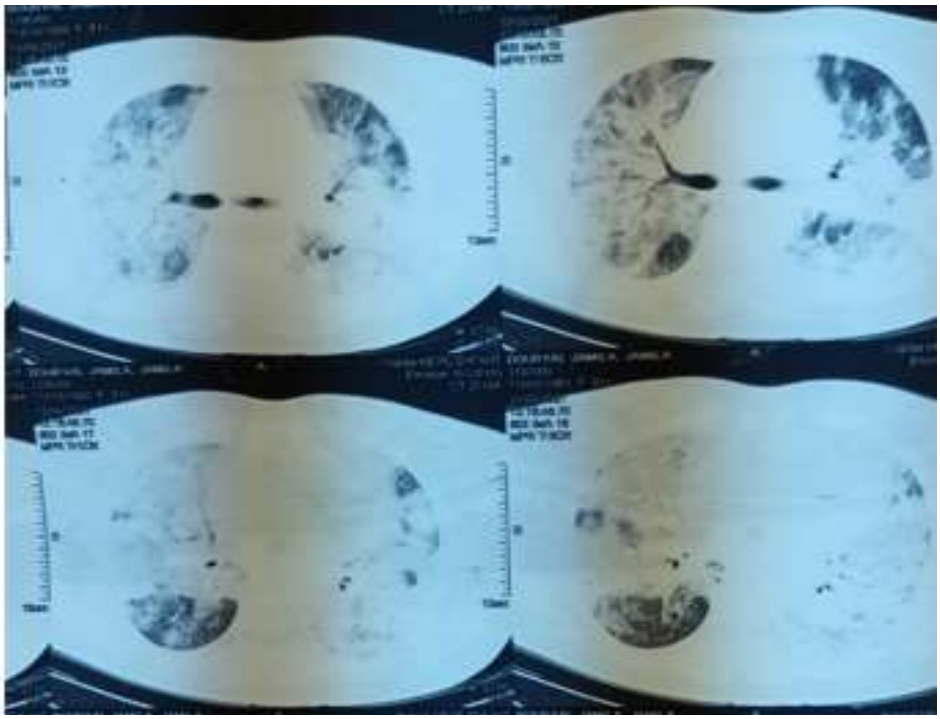

Figure 2:- Chest CT after 15 days of hospitalization and start of nintedanib treatment.

After 3 weeks the patient was able to walk with an oxygen concentration of up to 0.5 liter. Currently, she continues the protocol at home with a clear clinical improvement and good impact on daily activities.

Case 2:

This is a 40-year-old patient without particular pathological ATCDs, 3G / 3P / 2EV with a pregnancy estimated at 34 weeks of amenorrhea admitted to maternal intensive care for severe covid 19 pneumonia with pulmonary involvement between 25 and 50 % on chest CT.

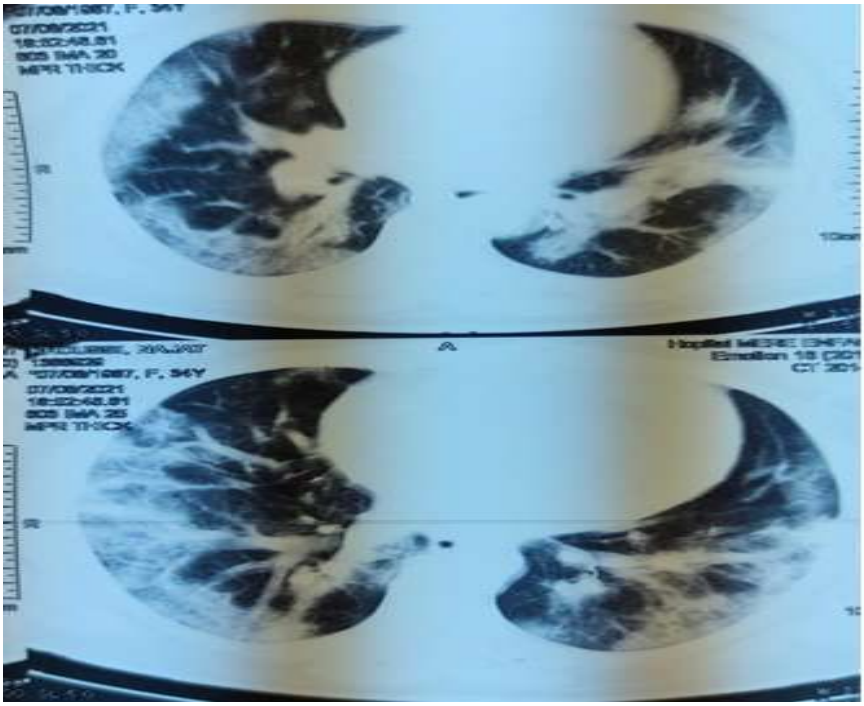

Figure 3:- Chest CT after admission.

The patient was placed on non-invasive ventilation with a Helmet helmet type continuously, and she received the azithromycin 500 mg / d + vitamin therapy + LMWH at curative dose + methylprednisolone 80 mg /d protocol.

Given the seriousness of the clinical picture, fetal extraction was considered under a high flow of oxygen 20 liters / min + half-seated position in the operating room under spinal anesthesia.

The development was marked by the alternation of non-invasive ventilation and high flow oxygen therapy with gentle and gradual weaning. However, the patient developed an addiction to 6l / min of oxygen. Follow-up chest CT noted an extension of the ground glass lesions and the appearance of thickening of the septal lines and bronchiolectasis.

Oral treatment with nintedanib at a dose of 300 mg / day in 2 doses was started, with armed biological monitoring every other day, without alteration of hepatic enzymes or renal function, haematological disturbances or other undesirable effects.

Currently the patient is still on nintedanib with marked clinical improvement and on 1l / min oxygen.

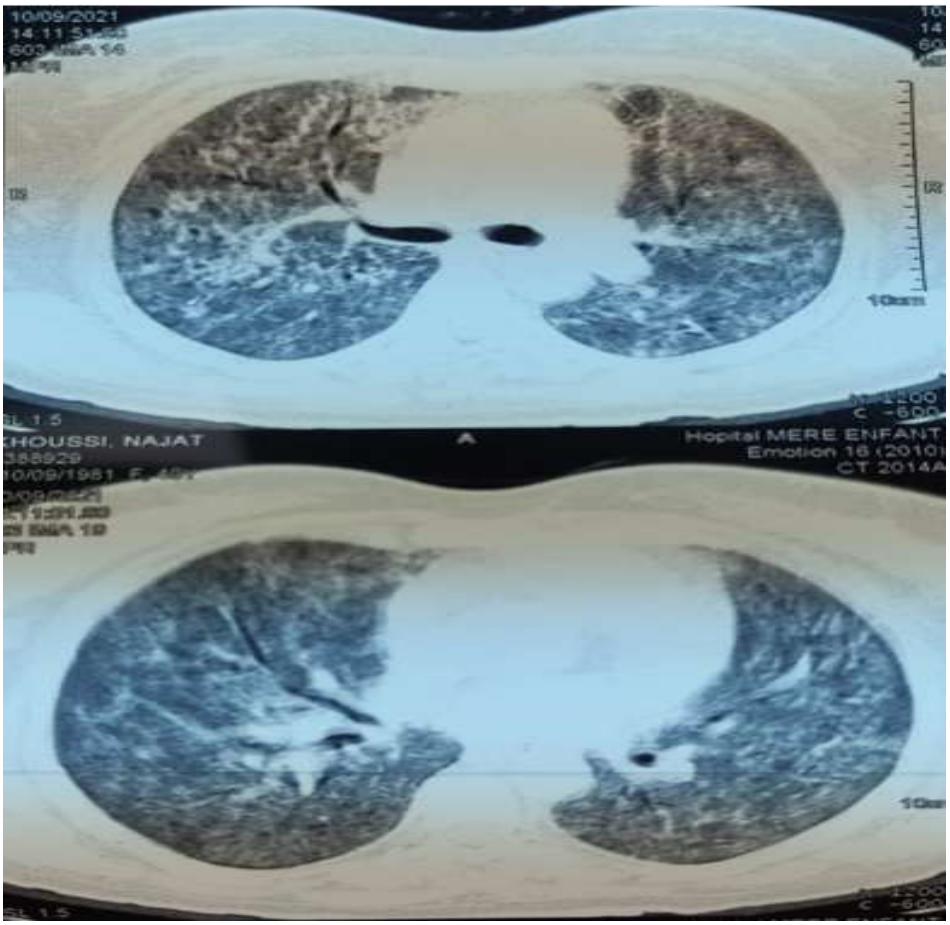

Figure 4:- Chest CT after 15 days of hospitalization and start of nintedanib treatment.

Discussion:-

Pulmonary fibrosis is a potentially fatal pathological consequence of acute and chronic interstitial lung disease characterized by failure to reconstruct the damaged alveolar epithelium, persistence of fibroblasts, and excessive collagen deposition.

Patients with COVID-19 pneumonia, especially severe or critical cases, are as likely to develop pulmonary fibrosis as SARS and Middle East respiratory syndrome (MERS) [6,7]. So, given the rapid evolution and expansion of the

COVID-19 pandemic, the notion of pulmonary fibrosis after recovery from COVID-19 will be important and will become a major health problem around the world [8].

Only one published Japanese intervention study has initiated this topic regarding the efficacy and safety of nintedanib for pulmonary fibrosis in severe pneumonia induced by coronavirus disease [9]. Thirty patients with COVID-19 underwent treatment with nintedanib. 30 patients not receiving nintedanib as historical control group. There were no significant differences in 28-day mortality between groups (23.3% vs 20%, p = 0.834). MV duration was significantly shorter in the nintedanib group (p = 0.046). The CT improvement showed that the percentages of areas of strong attenuation were significantly lower in the nintedanib group at VM release (38.7% vs 25.7%, p = 0.027). There were no significant differences in adverse events.

The study concluded that administration of nintedanib may offer potential benefits in minimizing lung damage in COVID-19.

Nintedanib is a tyrosine kinase inhibitor with selectivity for vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) receptors. It has been shown to be beneficial not only for idiopathic pulmonary fibrosis, but also for various other forms of progressive pulmonary fibrosis [10]. The plasma concentration of VEGF, PDGF and FGF has been shown to increase in COVID-19 patients [11], which suggests the efficacy of nintedanib.

In addition, this agent has been shown to decrease the expression of IL-1 and IL-6, which play a central role in the COVID-19 cytokine storm leading to pulmonary fibrogenesis [12]. Among the wide spectrum of progressive interstitial lung disease, treatment with nintedanib may inhibit the profibrotic pathways induced by SARS-CoV-2.

Conclusion:-

Post-COVID-19 fibrosis is one of the emerging complications of COVID-19 pneumonia and ARDS. It is estimated to be prevalent in about a third of hospitalized patients infected with COVID-19. Further studies are needed to investigate this event and test the effectiveness of drugs already tested (for idiopathic pulmonary fibrosis) such as antifibrotics for post COVID-19 fibrosis.

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