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Role of Antifibrotic Therapy in Pulmonary Fibrosis Due to COVID-19

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ABSTRACT

Background: It has been more than year of beginning of COVID-19 outbreak, the most serious complication of COVID infection is excessive increase in inflammatory mediators also known as cytokine storm which leads to formation of pneumonia in some patients. After resolution of pneumonia some amount of fibrosis develops which leads to decrease in quality of life and increased mortality. Nevertheless, in elderly patients a small % of fibrosis can be fatal. Therefore, as corona virus has affected several millions of people even though pulmonary fibrosis being a rare complication can cause huge no. of cases of pulmonary fibrosis, Several randomized control trials has been carried out till now for treatment of fibrosis, Perfenidone and nintedanib are approved as a treatment modality of idiopathic pulmonary fibrosis, it has been also useful in non-idiopathic pulmonary fibrotic diseases like interstitial idiopathic fibrosis studies are going out for effectiveness in post COVID pulmonary fibrosis.

Several other modalities are also being tested, drugs which help in decreasing the severity of cytokine storm such as steroids. Viral load can be decreased by using antiviral agents. Certain novel drugs are also being researched upon, so in this review article considering the impact of fibrosis on the covid population, cause of pulmonary fibrosis, prevention and treatment modalities has been discussed.

Key words: Post COVID, Pulmonary fibrosis, COVID-19, Pirfenidone, Ards, Nintedanib

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INTRODUCTION

In the month December of 2019 first news and reports came out of an unknown disease causing severe acute respiratory syndrome. This type of infection was first found in Wuhan (China) [1]. It was found later that the infection was caused by a novel strain of coronavirus family later this virus spread all around the globe and WHO declared it as pandemic on 11 March 2020.

After the initial reports from China and later from Italy showed that risk factor for pulmonary fibrosis was Age >60 yrs. H/O of smoking and co-morbidities such as diabetes and hypertension [2,3].

As of November 2021, 260 million has been affected by corona virus, so the burden of pulmonary fibrosis though being a rare complication is significantly high. There is rationale of using drugs licensed for IPF which are termed as antifibrotic therapy.

Novel antifibrotic strategies studies which have a range of antiviral and epithelioid protective effects in viral induced lung injury

LITERATURE REVIEW

Aim of antifibrotic therapy in COVID-19

- To avoid life threatening complications and lung injury in patients with active infection
- Accelerate healing process in resolved patients with reversible fibrosis [4].

In Corona virus infection there is unregulated autoimmune inflammatory reaction which cause increase in cytokines which is termed as cytokine storm. Pirfenidone has dual action of anti-inflammatory and anti-oxidant, a therapeutic strategy consisting of immunomodulatory IL-1, IL-6 inhibitors and antifibrotics can be important example of synergistic action.

Treatment option in COVID-19

ARDS is considered to be the most common cause of pulmonary fibrosis but studies show that ARDS in COVID-19 is not type of typical ARDS [5]. HRCT findings are not suggestive of typical ARDS there is significant increase in D-Dimer and other markers which suggest pro-

coagulants response of body after COVID infection [6]. In COVID there is injury to the alveolar epithelial cells and not endothelial cells [7,8]. So these factors suggest that specific drugs should be considered in COVID-19 rather than IPF drugs.

Spironolactone: Spironolactone is an aldosterone antagonist. Aldosterone is a mineralocorticoid receptor occurs in many diseases which causes increase in extracellular matrix which causes fibrosis of kidney, lung and cardiac [9]. Increased level of aldosterone also leads to increased BP and higher chances of CVS disease and alter inflammatory response [10].

In animal clinical trial spironolactone has shown to have antioxidant property which helps to protect organs from damage from free radical damage [11]. Patient treated with spironolactone showed decrease number of lymphocytes, eosinophils, neutrophils and macrophages in alveoli in comparison with spironolactone was not used. Spironolactone reduces activity of transmembrane serine protease 2 ($TMPRSS_2$). It has multiple activity like RAAS activity, anti-androgenic activity, anti-oxidant property, anti-fibrotic activity in its Renin Angiotensin Aldosterone System (RAAS) it reduces collagen synthesis thus by reducing RAAS signalling in corona associated pneumonia and related fibrosis.

Spironolactone has anti-androgenic action which is key to prevent Acute Lung Injury (ALI). It is important as adverse outcome of COVID-19 is associated with male sex, hypertension and obesity.

Anti-inflammatory activity of spironolactone is that it regulates inflammatory cytokine release of IL-2, IL-6, IL-15 and GMCSF which is responsible for hyper inflammatory state associated with COVID-19.

Antifbrotic action of spironolactone: spironolactone affects the extracellular matrix and effects collagen synthesis to prevent fibrosis. It also has antioxidant activity as it protects tissue from oxidizing stress triggered by COVID-19.

Steroids: The mechanism of steroids in viral pneumonia is to decrease host inflammatory response in lungs so significantly decreasing occurrence of ARDS and later pulmonary fibrosis. Coronavirus infection course is in 3 phases' immunosuppressive phase, normal phase and hyper inflammatory phase. Previous experience with SARS and MERS shows that it improved prognosis in viral pneumonia, adverse effects of steroids such as avascular necrosis of femoral head, hyperglycemia doesn't cause mortality and advantages outweigh the adverse effects [12]. Methyl Prednisolone is used in inflammatory phase of COVID infection and is found to decrease mortality [13]. Current research shows not to administer systemic steroids during initial period of infection as it decreases immunity and therefore increase in viral replication [14]. Corticosteroids is known to decrease radiological opacity by 25-30% but the trail had bias as the participant were young and already had less chances of having fibrosis.

Fibrinolytic therapy: In COVID patient it has been found that there is fibrin deposition in alveoli and parenchyma of lung which causes emboli due to micro clot formation which causes progressive respiratory arrest and right heart failure to increased pressure in pulmonary vasculature [15]. Therefore, thrombolysis increases ventilation by increasing the obstructed blood flow to the previously thrombosed portion of the lung.

By the studies it has shown that use of plasminogen activators has reduced case of ARDS and therefore mortality. In 2001 a study done by harduay and colleague proved that use of streptokinase in patients with ARDS reduced death rate from 100 to 70% without any significant side effect mostly bleeding disorders [16]. Human studies are not adequate regarding the use of TPA in virus related acute lung injury. In animal studies it was found that use of antifibrotic therapy *via* intra-tracheal and I.V use was useful [17].

Author of a publication suggested a dose of 25 mg of TPA in first 2 hrs and after that IV infusion of 25 mg TPA for another 22 hr [18]. The contraindication for the above therapy is same as that is present in case of stroke and myocardial infarction. TPA can be used in patients with ARDS who have PO_2/FiO_2 ratio <50 and PCO_2 >60 mmhg and in hospitals where ECMO is not available.

Antiviral drugs: Antiviral drugs are useful in decreasing viral load and hence the severity of disease and eventually fibrosis [19]. Hydroxychloroquine and Remdesivir seem to be the most important one. Hydroxycholoroquine an antimalarial which is used in COVID infection to reduce viral load by disrupting coronavirus cell receptor glycosylation [20].

Currently identified antiviral like remdesivir, lopinavir, ritonavir may inhibit RNA transcription and hence replication. Remdesivir was previously found useful in treatment of MERS infection [21].

The clinical trials on remdesivir which ended on 07/03/2020 [22]. In this trial remdesivir was given to patients with SARS COV+ve+SpO_2 <94%. During follow-up period of mean 18 days. 68% improved oxygen saturation. 57% patients on mechanical ventilation were extubated 13%; patients died.

Favipiravir an oral antiviral drug has been show to inhibit *in vitro* replication. Short time clinical study showed that use of favipiravir decrease viral clearance period from 11 to 4 days and improved radiological picture and hence decreasing incidence of pulmonary fibrosis [23]. Trial shows use of higher dose of favipiravir [24]. Anti parastitic agent ivermectin has also been studied upon and initial clinical trial had showed 99.98% reduction in viral load in 48 hrs.

Tocilizumab an IL_6 inhibitor is a monoclonal antibody used primarily in rheumatoid arthritis. It is found to decrease cytokine storm severity and hence lung damage and fibrosis [25].

Plasma therapy is also being studied and it is found that plasma therapy with the plasma of previously COVID infected person is found useful in decreasing viral load is initial part of treatment as antibodies are not formed so

readymade antibodies helps in controlling viral replication in initial period preventing severe COVID infection

Potential novel strategy

According to various clinical trials held colony stimulating factors like GM-CSF can accelerate elimination of viruses [26].

Some of the drugs like nintedanib and pirfenidone which are approved for idiopathic pulmonary fibrosis are being tested for COVID related fibrosis treatment. Nintedanib a typrosine kinase inhibitor is an oral drug. It acts on FGF, PDGF and VEGF receptors which results in downregulating fibroblast and myofibroblast cells and cells which are involved in angiogenesis in lung [27].

Pirefenidone is an anti-inflammatory, antifibrotic and anti-oxidant property. It down regulates inflammatory cytokines. It down regulates TGF-beta expression. There had been various trails on nintedanib.

One of the trial named INPULSIS nintedanib reduced exacerbation of IPF. In INBUILD trial forced vital capacity showed positive impact on using nintedanib A alkaloid,tetrandrine which is found useful in lung cancer [28,29]. Can be used in treatment of fibrosis, it affects reactive oxygen species, calcium channel and caspase pathway. Drugs used in liver fibrosis namely Fuzheng Huayu formula, that contains 6 Chinese herbs is under trial. It comes in tablet form and is approved for liver fibrosis it includes 6 herbs Radix Salviae Miltiorrhizae, Cordyceps Mycelium Powder, Semen Persicae, Pollen Pini, Gynostema Pentaphylammak and Fructus Schisandrae, Chinensis. It comes in capsule and tablet form. It was initially found useful in interstitial lung fibrosis and fibrosis in COVID-19 is of similar type it is thought it would be beneficial for patients of lung fibrosis caused due to COVID infection.

In Hyperbaric oxygen therapy pure 100% oxygen is given at 1.5 atm for 5 min, mesenchymal stem cell and human purified amniotic fluid therapies are under trial. Human purified amniotic fluid therapy is sued as it has been found that amniotic fluid has anti-inflammatory, antibacterial and has regenerative potential. Amniotic epithelial cells express stem cell $SSEA_3$, $SSEA_4$, TRA_1-69, TRA_1-80, OCT_4 and nanog. Amniotic fluid cells have good cell-differentiation potential it also has immunomodulatory properties that prevent hyper inflammatory response commonly seen in severe cases of COVID-19 but due to lack of knowledge in stages of viral replication in association with use of amniotic fluid we cannot exactly say at what stage of viral replication amniotic fluid would cause effect.

Simtuzumab: This drug is anti-lysal oxidase ($LOXL_2$). It is known that these enzymes help in facilitating crosslinking of collagen molecules. $LOXL_2$ levels are found to be increased in idiopathic pulmonary fibrosis and other fibrotic disorders.

Increased level of $LOXL_2$ has been shown to cause cell proliferation. $LOXL_2$ can be antagonized by monoclonal antibody AB0024 which leads to decreased fibroblast and down regulation of TGF-B the trial for simutuzumab (GS6624) phase II has completed [30].

Mesenchymal stem cell therapy

Mesenchymal Stem Cell therapy also known as (MSCS) has effect directly on the lung injury site caused due to inflammatory cytokines due to COVID-19. During various trials it has been found that mesenchymal stem cells have some unique cytokines that has immunomodulatory and anti-fibrotic property. MSC can be isolated from teeth, bone marrow, umbilical cord and placenta. MSC secrete factor such as angiopoietin 1, IL-10, hepatocyte growth factor precursor ($ANGPT_1$), Epidermal growth factor. HGF prevents tissue fibrosis by inhibiting TGF-B induced phosphorylation formation of collagen is stopped so pulmonary fibrosis is prevented.

Remdesivir: Remdesivir a drug approved for EBOLA infection is a nucleoside analog drug which inhibits transcription of viral RNA by inhibition of RNA dependable RNA polymerase. As we already know TGF-B_1 signalling pathway is important for the cascade of fibroblast activation to cause pulmonary fibrosis. Therefore, a trial was conducted to check whether remdesivir can regulate TGF-B_1/smad and non smad pathway in pulmonary fibrosis. After the experiment we found that remdesivir significantly reduces the activation of TGF-B_1/smad/non smad signalling hence reducing pulmonary fibrosis [31].

Pirfenidone: Pirfenidone is 5 methyl 1 phenyl 2 pyridone having anti-fibrotic, anti-inflammatory action and is approved for idiopathic pulmonary fibrosis. Pirfenidone acts by downregulating cytokines TGF, PDGF, TNF alpha. It is also a reactive oxygen scavenger and also it downregulates ACE receptor expression which is main receptor of COVID-19. Perfinedone also has anti-apoptotic and anti-fibrotic properties.

Anti-inflammatory properties of Pirfenidone: it inhibits TNF alpha secretion and inhibits lipopolysaccharide induced inflammation by blocking $NLRP_3$ activation.

Anti-fibrotic effect: Pirfenidone inhibits TGFB-1 induced fibronectin synthesis. As we already know TGF B-1 plays key role in causing fibrosis of lung. Pirfenidone inhibits collagen I fibrin formation by reducing collagen bundles, it also upregulates RGS_2 which helps in resolving pulmonary fibrosis.

Protection against oxidative damage: In COVID there is hyper inflammatory response and WBC free radical formation, damage to proteins, apoptosis of cells and oxidative stress due to cytokine storm. Pirfenidone has antioxidant action and prevents fibrosis.

Anti apoptopic action of pirfenidone: In virus illness like pox virus, corona virus it is seen that there is Fat dependent apoptosis resulting in inflammatory reaction. Pirfenidone decreases this type of apoptosis.

Downregulation of ACE receptor expression: it is already known that COVID 19 SARS virus enters human body from ACE receptors it has been identified that pirfenidone inhibits AT_1R/P_{38} MAPK pathway leading to decreases in ACE, angiotensin II type 1 receptor. This will not only protect cells from developing fibrosis but will also decrease entry of viruses into human body through ACE receptors.

Colchicine: It is an approved drug used mainly for gout, behcet disease etc. it works by preventing microtubule assembly and inhibiting generation of cytokines, leukotrienes and chemotaxis. In respect to COVID colchicine may prevent lung fibrosis by the anti-inflammatory action of drug, its anti-inflammatory action is due to multiple mechanisms out of which the main mechanism of action is to bind tubulin molecule resulting in inhibition of migration. Colchicine inhibits cytokine storm by inhibition of IL-1, IL_6, and Il-18 because colchicine can interfere with $NLRP_3$ inflammatory molecule which has main part in cytokine storm. Colchicine also inhibits superoxide anion production and histamine release. Colchicine at low dose 0.5 mg-1 mg per day is found to be safe even after decades of use. There are some side effects such as G_I complications, bone marrow suppression, and myotoxicity. It should not be given with cytochrome P_{450} inhibitor such as macrolides because it increases toxicity. So after many trials it has been found that colchicine 0.5 mg BD given in early COVID infection would prevent progression from stage 2 to stage 3 [32].

Azathioprine, N-acetyl cysteine and corticosteroid

N-acetyl cysteine is anti-oxidant mainly used in paracetamol poisoning. It is a precursor of glutathione production and thus causes anti-oxidant effect decreasing fibrosis. A trial named PANTHER-IPF was conducted by giving N acetyl cysteine 600 mg TDS along with prednisolone, azathioprine and N acetyl cysteine. The result showed that FVC increased after 60 weeks. It has been shown that treatment with triple therapy has positive impact when duration of treatment is greater than 12 months.

Cyclophosphamide: It is a drug from nitrogen mustard group and is an alkylating agent it is given orally and metabolism occurs in liver causing cytotoxic compounds which supress lymphocytic function. The decreased lymphocytes cause less fibrosis.

Adverse effects: it causes immunosuppression leading to bone marrow suppression, hepatotoxicity, it also causes increase in malignancy.

Lung transplant: Lung transplantation is the last resort for pulmonary fibrosis patient. It is potentially lifesaving in cases of non-responding respiratory failure. Pulmonary fibrosis is aberrant disorganised deposition of collagen material in the alveoli of lungs due to which this part of lung the oxygen dissociation does not occur leading to hypoxia. There are concerns regarding the graft rejection in lung transplantation. Recipients of lung transplantation are given 3 drug immuno suppression which includes antimetabolite, calcineuren inhibitors and steroids.

DISCUSSION

So after extensive research it was evident that COVID had the tendency to cause idiopathic pulmonary fibrosis. Initial studies for spironolactone were done on animals and were found effective [11] but human studies are lacking.

Steroid are known to decrease the severity of progression of COVID infection, but studies related to fibrosis had bias as young people were involved which has less tendency to have fibrosis [13] Clinical trials were done for remdesivir which resulted 68% people improving. Favipiravir also decreased viral replication [24].

Ivermectin decreased viral load by 99% in 48hrs in the clinical trial. Tocilizumab reduced the inflammatory response of body hence decreasing severity of fibrosis formation [25].

The INBUILD Trial for nintedanib showed positive effect [27]. Pirfenidone trial also decreased the lung fibrosis. PANTHER IPF trial showed positive effect in this trial triple therapy was used with drugs prednisolone, azathioprine and N acetyl cysteine.

CONCLUSION

COVID-19 is an extremely seriously disease in high risk patient. It causes severe acute respiratory illness which may lead to pulmonary fibrosis. Given the number of individuals infected with COVID-19, even rare complication like lung fibrosis may affect a significant amount of population. As discussed above various drugs has been used in clinical trials. All these drugs affect various mechanisms which are responsible for lung fibrosis after COVID, but till date definite treatment modality has not been established yet. Pirfenidone and Nintedanib is being used in fibrosis cases but it effectivity has not been fully proven.

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