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Idiopathic Pulmonary Fibrosis

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ABSTRACT:
IPF is a destructive condition with a poor prognosis. In this review, we have systematically reviewed the cause of IPF factors like smoking, Genetic Factors, Environmental Exposures etc.. We have mentioned about the drugs that causes fibrosis are cytotoxic drugs (Bleomycin, Carmustin, Busulfan, Mitomycin) and Non-cytotoxic drug (Amiodarone). We have explained the usual symptoms like dry cough, dyspnea and various risk factors like genetic, aging, male sex, cigarette smoking. The classical and online literature were studied in order to collect the data relevant to various comorbidities like Pulmonary Hypertension, Emphysema, Lung Cancer, GERD, Sleep Apnea etc.. We have highlighted the recent advances in diagnosis and therapeutics used in the treatment of IPF, which includes Non-Pharmacological treatment. The classical and online-literature were studied in order to compile the data which includes the electronic search engine such as Scopus, Google Scholar, Sci Finder, Web of Science , Pubmed etc. The scientific data shows that at present, there are different families of oral and injectable drugs, available for the treatment of IPF which has deleterious side effects. Hence, we need to develop a novel, safety and effective agents that will improve the quality of life of IPF patients.
KEY WORDS: IPF (Idiopathic Pulmonary Fibrosis), HRCT (High Resolution Computer Tomography), Smoking, Pulmonary Rehabilitation, Palliative Care.

I .INTRODUCTION:

Idiopathic Pulmonary Fibrosis is a progressive, chronic, fibrotic lung disease[1] and it is a non-neoplastic Pulmonary Disease characterized by the thickening and the formation of scar tissue in the lungs[2]. It is a component of 200 Interstitial lung disease [3].Altered Extracellular Matrix is replaced by the healthy tissue and destroy alveolar architecture which leads to reduced lung compliance, altered gas exchange, Respiratory failure and death [1]. It need early recognition and intervention with supportive care and pharmacological agents to prevent it's progression[4]. It is distinguished by the interstitial infiltrates affecting the bases of lung by slowly increasing dyspnea and exacerbate the pulmonary function. It is also called as cryptogenic fibrosing alveolitis, family of idiopathic pneumonia[5]. It is more common in men than in female and rare in younger men [6].

II.ETIOLOGY:

i. It is caused by many triggers such as chemicals, allergens, radiation[6]. Environmental Exposures such as asbestos, microorganism, viruses etc.[7]
ii. Older age.
iii. Cigarette smoking.
iv. Male sex.
v. Genetic factors[1]
vi. The host defence [MUC 5B, ATP11A, TOLLIP].
vii. Telomere maintenance [TERT, TERC, OBFC1].
viii. Epithelial barrier function [DSP, DPP9].
ix. Unknown cause – Idiopathic Pulmonary Fibrosis.

III.DRUG ASSOCIATED WITH PULMONARY FIBROSIS

Antineoplastic:

Cancer chemotherapeutic agents cause a pulmonary fibrosis. Drugs are directly toxic to the lung and slow dose response relationship. Bleomycin, Busulfan and Carmustine established to dose response [8]. Bleomycin and Busulfan shows threshold cumulative dose[9]. Bleomycin, Busulfan and Mitomycin are the evidence for Synergistic toxicity with radiation [8]. Multiple drug regimen such as carmustine, mitomycin, cyclophosphamide, bleomycin and Methotrexate cause increased lung toxicity.

Nitro Ureas:

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BCNU [Carmustin] are the highest incidence of pulmonary toxicity [8]. BCNU inhibits glutathione reductase required to restore the enzyme Glutathione by reducing glutathione tissue stores. The risk of death was considerable higher for women receiving the dose greater than 475 mg/m2 than men [10]and no risk of death in patient receiving the dose 475 mg/m2 in women. When patient receiving high doses in other Nitroureas, Lomustine and Semustine cause lung damage [8].

Bleomycin:

The incidence of bleomycin is 4% affected by the risk factors such as cumulative dose, age, high concentration of inspired oxygen, radiation therapy and Multidrug regimen specifically with cyclophosphamide [11]. Bleomycin generates superoxide anions, and the lung toxicity is increased by radiation and hyperoxia [8]. Bleomycin affect collagen deposition by its stimulation of fibroblast growth[8]

Mitomycin:

Mitomycin produces pulmonary fibrosis and toxicity is enchanted by the oxygen and radiation therapy [8].

Alkylating Agents:

Cyclophosphamide, Chlorambucil, Uracil, Melphalan associated with pulmonary fibrosis. Nitrogen mustard and Tiotepa don't cause fibrotic pulmonary toxicity[8].

Antimetabolites:

Methotrexate induce Pulmonary toxicity and result in hypersensitivity [12]and occur three or more years following Methotrexate therapy[13].

Non Cytotoxic Drugs:

Pulmonary fibrosis linked to Ganglionic-blocking agent

Amiodarone:

It is a benzofuran derivative that is used for treatment of supra ventricular and ventricular arrhythmias can cause pulmonary fibrosis [14]. The mechanism of amiodarone induced pulmonary toxicity is Multifactorial and it's metabolite can damage lung tissue directly by a cytotoxic process or indirectly by immunologic reactions [15].

IV RISK FACTORS:

Extrinsic factors

1.Cigarette smoking

Cigarette smoking is the high risk for occurrence of familial Interstitial Pneumonia. Nicotine produce TGF- beta by itself. [16]

2.Environmental Exposure

Environmental exposure is associated with IPF include wood dust metal dust (brass, lead, and steel), vegetable dust, livestock dust, Asbestos, silica, sand and stone. [16]

Intrinsic factor

1.Aging

Middle age and old age people may contribute the risk of IPF. In peripheral blood and the lung, the telomere length is shorter in IPF patient. The Molecular basis shows deregulated reactions to the aging lung include a senescent phenotype in IPF lung fibroblasts. [16]

2.Male Sex

Men are more prevalence in IPF due to inhaled exposure such as Tobacco, smoking or Occupational exposure.[16] Animal model (mice) with bleomycin demonstrate that the male mice are more susceptible to IPF disease and shows that male sex hormones are stimulated to fibrosis and female sex hormones are effective against pulmonary fibrosis [17].

3.Genetic factor

Surfactant proteins C, A1, A2, A3 affect the alveolar stability. Gene associated with telomerase function TERT (Telomerase Reverse Transcriptase), TERC (Telomerase Reverse Transcriptase Component), DKC1 (Dyskeratosis congenita), TINF2 (TERF1- Interacting nuclear factor 2), PARN (Poly (A) Specific Ribonuclease) RTEL1 (Regulator of Telomere Elongation Helicase 1) affect the cell Senescence. Human airway mucin MUC5B (Mucin 5B), MUC 2 (Mucin 2), TOLLIP (TOLL Interacting protein), TLR 3 , HLA- DRB1 , ILIRN (Interleukin 1 receptor antagonist), IL8 affect the best defence. DSP (Desmoplakin), DPP9 (Dipeptidyl Peptidase 9) affect the cell- cell adhesion.[16]

V COMORBIDITIES:

IPA is associated with number of Comorbidities such as Pulmonary Hypertension, Emphysema, lung cancer, coronary artery disease, GERD, Sleep disorder, Psychiatric disorder[18].

1.Pulmonary Hypertension (PH):

Pulmonary Hypertension is defined as a mean pulmonary artery pressure (PAP) higher than 25 mm Hg in the presence of pulmonary capillary wedge pressure lower than 15 mm Hg. Pulmonary hypertension in IPF Patient is more common in any stage of the disease or in the combined pulmonary fibrosis and Emphysema Syndrome [18,19] . PH is present in approximately 20 to 50 % of patient with IPF at the time of the lung transplantation [19, 20].

2.Emphysema:

The term " Combined Pulmonary fibrosis and Emphysema " (CPFE) is

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characterized by the presence of features of Centrilobular or para septal. Emphysema in the upper lobes and pulmonary fibrosis in the lower lobe [21]. Male gender with smokers is associated with CPEF. The patient with CPFE is complicated with pulmonary hypertension and lung cancer [19].

3.Lung Cancer:

Pathogenetic mechanisms that cause lung cancer in IPF Patient include chronic inflammation, cytokine mediation, cellular injury and genetic damage due to recurrent inflammation and repair. The Common mediators cause both lung cancer and IPF [19].

4.GERD:

GERD is more prevalence in IPF patient who have experienced lung transplantation [22]. Pathologic reflux is common in IPF Patient and the reflux is associated with abnormal esophageal peristalsis, hypotensive lower esophageal sphincter and often into the proximal esophagus [23]. The presence of Hital Hernia alone was not related with decreased lung function and it is associated with Gastro Oesophageal reflux and Cause IPF [24].

5.Sleep Disorder:

Patient with IPF having moderate to severe Obstructive sleep Apnea (OSA)[25]. Nocturnal Hypoxemia occur in untreated OSA Patient and Correlates with Survival and increased Right Ventricular Systolic pressure [25,26].

6.Coronary Artery Disease:

Coronary Artery Disease also called as Atherosclerotic heart disease. The pathologic similarities between Atherosclerotic lesion and Fibrotic lung disease are linked. Excessive inflammatory and fibro proliferative response to Endothelium and smooth muscle of the arterial wall results in Atherosclerosis and this are parallel to the fibrotic lung disease [27].

7.Psychiatric Disorder:

Anxiety or depression is common in patient with chronic illness Disorder IPF. Patient undergo dyspnea and fatigue and also have Psychiatric symptoms due to medication (corticosteroids) cause mood disturbances such as Mania, depression and mood disability occur within first two weeks of treatment. To screen IPF patient ask if you are feeling down, depressed or hopeless in past month and also you bothered any pleasure and small interest in doing works. Patient respond with “YES" and should be evaluated [18].

VI CLINICAL PRESENTATION:

- Dry cough
- Fatigue
- Dyspnea
- Digital clubbing
- Weight loss
- Leg edema
- Chest discomfort[30]
- With coarse “Velcro like crackles audible on auscultation over lower lobes[32]

VII DIAGNOSIS

A detailed patient history on physical examination should be taken. Patients history and physical examination along with radiologic studies and lung biopsy to forbid alternative diagnosis [28].

Physical Examination:

The Physician should examine the patient lungs carefully to find any abnormal sounds. If there any extraordinary lung finding, a number of tests should conducted [28].

Chest X ray:

It is the baseline diagnosis and shows the scar tissue typical of pulmonary fibrosis [28].

High Resolution CT [HRCT]:

HRCT is a optimistic diagnosis for IPF patient .It is based on the presence of bilateral, predominantly subpleural and basal reticular opacities with associated traction bronchiectasis and honeycombing in the absence of small nodules or extensive ground glass opacity [29]. Microscopically, IPF is characterized by the presence of Interstitial inflammation, fibroblastic foci and established fibrosis and honeycombing coexisting with areas of normal lung parenchyma.[29]

Ground Glass Predominance:

It is characterized by gradual deterioration over several months to years, with progression of parenchymal abnormalities on HRCT.[29]

Consolidation and Nodules:

It is not common radiologic manifestation in the absence of complication such as acute aggrevate superimposed infection or pulmonary carcinoma. Patient with IPF have increased risk of tuberculosis, present in solitary nodule. HRCT shows small calcified nodular opacities typically confined to areas of fibrosis [29].

Distribution of abnormalities:

The characteristic basal and peripheral predominance of the abnormal on HRCT Scan is an important indication for the diagnosis of IPF. IPF patient show severe in the lower zone and fibrosis is present in the upper lobes and increased the specificity of HRCT in the diagnosis.[29]

Pulmonary Function Test:

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Restrictive Ventilatory defect and decreased diffusion capacity for carbon monoxide are the typical findings in pulmonary function test in patient. Vital capacity, functional residual capacity, total lung capacity and forced vital capacity.[30]

6 Minute Walk Test:

The 6MWT is a marker of functional exercise capacity used in the Initial and clinical Assessment of patient with IPF. During 6MWT, the patient with IPF who desaturate to less than 88%, decrease in DL is a strong prognosis of increased mortality.[30]

Broncho Alveolar Lavage [BAL]:

BAL has been a vastly useful tool in IPF. A salt solution is injected into air sacs in the lungs and sectional out immediately for analysis.[28]

Surgical Lung biopsy:

A surgical lung biopsy specimen is obtained through either an open lung biopsy or Video – Assisted Thoracoscopic Surgery [VATS]. VATS is commonly used due to less morbidity and have shorter duration to stay in hospital compared with open lung biopsy. VATS used to monitor the lungs while removing tissue samples from the lungs.[30]

Pulse Oximetry:

Pulse Oximetry measures the percentage of Oxyhemoglobin saturation in the blood.[31]

VIII.TREATMENT:

General approaches:

The factors to control the beginning treatment include:

- ✓ Consider the currently available anti-fibrotic treatments.
- ✓ Avoid factors the aggregate the disease (GERD, respiratory infection, pulmonary hypertension, smoking).
- ✓ Treat the symptoms mainly cough and dyspnea.
- ✓ Lung transplant.
- ✓ Final phase treatment – palliative care[33]

Non Pharmacological Treatment:

General measures:

Quite smoking:

Smoking increases the risk of comorbidities such as lung cancer and emphysema in chronic lung disease. So, quitting smoking is a keystone for the management of IPF patient.[33]

Vaccination:

Vaccination against Influenza and Pneumococcal infection should be encouraged in all patients with IPF.[33]

Nutritional Intervention:

Proper intake of micronutrients and anti-inflammatory diet is consider as Diet therapy for IPF patients.

Antioxidant:

Intake of antioxidant should be increase. Antioxidants may protect the body against free radicals. It includes all types of leafy green, sweet potatoes, broccoli and other Cruciferous veggies, tomato, citrus, green tea and sea vegetables etc. Avoid refined and processed foods such as fried foods and hydrogenated fats, dairy products, spicy food, soda etc. For GERD include bone broths which provide amino acids, minerals and electrolytes for hydration. For Reflux symptoms, use apple cider vinegar. Omega 3 fatty acids from flax, salmon, sardines and probiotic foods such as vegetables and yogurt are also recommended. Lean protein - it gives the vitamin and minerals to keep metabolism efficiently. This is important to assure that this food does not produce a great damage already compromised immune system such as fish, meat and poultry. The quality of the food you eat greatly is the impact the ability of the body to get oxygen into the blood and throughout the body. Omega 3 fatty acids, lean protein, phytonutrients are the important foods for the management of pulmonary fibrosis.[34]

Oxygen Therapy:

Oxygen Therapy reduces breathlessness and increase physical capacity by improving the gas exchange. Ambulatory oxygen is used for Comorbidities such as pulmonary hypertension and Right Heart Failure.[33]

Support Therapy:

High Flow Nasal Cannula (HFNC) Oxygen:

It provide high flows FiO2 (Fraction of Inspired Oxygen) delivery. Humidification can improves secretion clearance and maintain the mucosal integrity. It requires less training and can be applied outside ICU's compare to NIV.[33]

Non – Invasive Support (NIV):

It is an significant role in improving dyspnea.[33]

Extra corporeal Membrane Oxygenation:

It is also called as Veno –Venous ECMO and used in patient while waiting for lung transplantation [33]

Lung Transplantation:

The following situation are recommended for patient such as

1. Decline in FVC greater than 10 % during 6 months of follow up.
2. Decline in DLCO (Diffusing Capacity For Lung for Carbon monoxide.

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3. Desaturation to less than 88% or distance less than 250 m on 6 MWT or 450 m decline in 6 MWT distance over a 6 month period.
4. Presence of Pulmonary hypertension on Right heart Catheterization or 2- Dimensional Echocardiography.
5. Hospitalization due to Respiratory decline , Pneumothorax or acute Exacerbation.[33]

Pulmonary Rehabilitation:
Impact of pulmonary rehabilitation in IPF
Increase exercise capacity
Decrease dyspnea
Decrease depression
Decrease anxiety
Decrease fatigue
Increase QOL (Quality of Life)
Increase cognitive function

Palliative Care:

The Quality of life of the patient as well as that of this family and caregivers is managed by the multidisplinary care approach such as control of symptoms and physiological care.[33] WHO definition "Improves the Quality of life of patient and their families facing the problem associated with life threatening illness, through the prevention and relieve serious health related suffering be it Physical, Psychological, Social or Spiritual is a global Ethical Responsibility".[35] Depression and Anxiety is more prevalent in patient with IPF.

Pharmacological Treatment:
Pirfenidone: (5 Methyl -1- Phenyl-2-[1H]-Pyridone)

It is an antifibrotic agent and have broad spectrum anti inflammatory activity. This drug shown limited toxicity and improvement in patients.[36] FDA recommended dose is 2403 mg daily.

The therapy is initiated with,

- Day 1-7 → 267 mg orally three times per day (801 mg/day)
- Day 8-14 → 534 mg orally three times per day (1602mg/day)
- Day 15 and thereafter (maintenance) 801 mg orally three times per day not to exceed 2403 mg /day [37].

It inhibits fibroblast proliferation and attenuated Transforming Growth Factor (TGF) – β induced α-SMA (Smooth Muscle Actin) and Procollagen expression at both mRNA and protein levels. Pirfenidone reduced TGF-β induced phosphorylation of Smad3, P38 and Akt, key mediators of TGF-β pathway[38].

Adverse Reactions of this drug includes Nausea, Rash, Upper Respiratory Tract Infection, Photosensitivity, Diarrhea, Insomnia, and Arthralgia.

Cautions* – Conduct liver function test (ALT, AST and Bilirubin) before initiating, monthly for 6 months, dosage modification, discontinuation necessary for liver enzyme elevation.

*For photosensitivity and rash reported – avoid exposure to sunlight and sunlamps and wear protective clothing daily.[39]

Efficiency – Pirfenidone is more efficacious in the early stage than in advanced stage of IPF. It reduce the decline in the forced vital capacity.[40]

Nintedanib:

It is an indolinone derivative derived from a chemical lead optimization programme designed for receptor based Tyrosine Kinase inhibitor. It is designed as an Anti Angiogenic drug that binds to the intracellular ATP binding pocket of Fibroblast Growth Factor Receptor (FGFRs), Platelet – Derived Growth Factor Receptor (PDGFRs) and Vascular Endothelial Growth Factor Receptor(VEGFRs) resulting in blockage of the autophosphorylation of these receptors and the downstream signalling cascades [41].

Adverse Reactions of this drug includes Diarrhea, Nausea, Abdominal pain, Elevated liver enzymes, Vomiting, Hypertension, MI, Hypothyroidism.

Cautions – Not recommended in patients with moderate to severe hepatic impairment , Quit smoking , reduce the dosage if diarrhea occur.

Initiated dose – 150 mg orally q12 hrs [42].

Corticosteroids:

Corticosteroids are given in combination with Immunosuppressants and it is called as "GOLD STANDARD" treatment in IPF patients [43]. Corticosteroids reduce the "Ground Glass Opacities" that is found during HRCT.[44]

Corticosteroids suppress Neutrophil and Lymphocyte migration into the lungs, alter alveolar macrophage function, decrease the level of immune complexes

Adverse reactions of this drug include Weight gain, Hyperglycemia, Osteoporosis, GI effects[45].

Corticosteroid – Prednisolone
0.5 mg/kg/day orally 4 weeks
0.25 mg/kg/day orally 8 weeks reduce dose to 0.125 mg/kg/day (or) 0.25 mg/kg/alternative days.[46]

Corticosteroid is used in combination with Azathioprine and Cyclophosphamide

Azathioprine: It is a Purine analog. It inhibits adenine deaminase, impairs the proliferation of

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cells especially leukocytes and lymphocytes. 2-3 mg/kg/day. Maximum dose: 150 mg/kg/day. Initial dose: 25-50 mg/day. Increase the dose by 25-50 mg every 1-2 weeks.

Cyclophosphamide: It is an Alkylating agent. It is activated in liver to cytotoxic compound that suppress lymphocytes. 2 mg/kg/day. Maximum dose: 150 mg/day. Initial dose : 25-50 mg/day. Increase the dose by 25-50 mg every 1-2 week.[46]

N – Acetyl Cysteine:

N – AcetylCysteine is a innovative treatment for IPF.[47] N-Acetyl Cysteine is a standard therapy with Prednisolone+Azathioprine. N-AcetylCysteine is administered orally as 600 mg three times daily.[48]

N – AcetylCysteine increases the synthesis of glutathione, a potent antioxidant, decrease the fibrotic response, and slows progression by inhibiting epithelial mesenchymal transition.[47]

Colchicine:

Colchicine inhibits secretion of collagen and suppress the fibroblast growth factor [49].

D – Penicillamine:

D-Penicillamine inhibits collagen turnover, collagen synthesis and attenuate collage deposition by interrupting cross-linking of collagen molecule[50].

Angiotensin – Converting Enzyme Inhibitor (ACEI) and Statins:

ACEI and Statins are the antifibrotic properties and have no significant difference in survival or improvement in patients with IPF receiving ACEI and Statins and between the patients not receiving these drugs.

Immunomodulators:

Interferon γ – 1b

IFN – γ is an inflammatory cytokine with a number of inhibitory effects on fibroblast. Dose is initiated with 100μg three times/week for 2 weeks followed by 200μg three times/week[50].

Bosentan – Endothelin Receptor 1 Antagonist:

Bosentan – Non selective ET (A) and ET (B) Receptor Antagonist. The endothelial cell derived Endothelin -1 (ET-1) is a potent mitogen for endothelial cells, vascular smooth muscle cells and tumour cells. It is upregulated in IPF lungs and mainly expressed in endothelial cells.[50] Dose: 62.5 mg twice daily.

Imatinib Mesylate:

It is a C-Abl tyrosine kinase inhibitor and also inhibits activation of Platelet Derived Growth Factor Receptor (PDGFR). Dose: 600 mg orally once per day.

FG – 3019 (Pamrevlumab)

It is a human anti-CTGF IgG1 monoclonal antibody and block the profibrotic activity of CTGF (Connective Tissue Growth Factor) in IPF patients.

The role of CTGF is triggering the production of collagen and fibronectin which cause scarring and thickening of the lungs.[50]

Anti-Leukotriene Drug:

Leukotrienes are derived from 5-lipoxygenase pathway of arachidonic acid metabolism. LTs are profibrotic by induction of fibroblast migration, proliferation and matrix, protein synthesis. LTB_4 and LTC_4 levels are increased in IPF patients. Zileuton is a 5- lipoxygenase inhibitor and it is under a trial.

IX CONCLUSION:

IPF is the thickening and scarring of the lung tissue. The common cause of IPF is unknown yet there are some other causes like drugs, environmental factors and genetic factors etc. Increased age and male sex are more prevalent to IPF. Drug like Carmustine has the highest incidence of pulmonary toxicity. Mitomycin, cyclophosphamide and Chlorambucil produce pulmonary fibrosis. The metabolic product of Amiodarone can cause damage to the lung tissue. Drug induced pulmonary fibrosis can be prevented by discontinuing the drug and managing the symptoms. The most frequent risk factor of IPF is smoking. Comorbidities like GERD are common and is must be managed by treating them with anti-reflux therapy. Cardiovascular diseases and lung cancer are difficult to treat in IPF patients. HRCT plays a major role in the diagnosis of IPF. Other diagnosis includes physical examination, pulmonary function test etc. Palliative care improves the quality of life of the patients. Pulmonary Rehabilitation increases the cognitive function, quality of life and decreases dyspnea, anxiety and depression. Oxygen therapy reduces shortness of breath and improves gas exchange. Pirfenidone inhibits the fibroblast proliferation and used in the treatment of IPF. Corticosteroids (Prednisolone) in combination with Azathioprine and Cyclophosphamide are used to treat IPF. N-AcetylCysteine is considered as the innovative treatment for IPF.

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