JOURNAL MEDICAL INFORMATICS TECHNOLOGY
medinftech.org ISSN 2988-7003 (online)

Renewable Therapy Potential of Allogeneic Bone Marrow-Derived Mesenchymal Stem Cells for Idiopathic Pulmonary Fibrosis

Aloysius Krishartadi Damar Bawono[1], Gasela Zalianti Balqis[2], Rais Amaral Haq[3], Ratna Dewi Puspita Sari[4], Winda Trijayanthi Utama[5], Suryani Agustina Daulay[6]*

[1,2,3] *Medicine Undergraduate Study Program, Faculty of Medicine, University of Lampung, Indonesia*
[4] *Obstetric and Gynecology Diseases Department, Faculty of Medicine, University of Lampung, Indonesia*
[5,6] *Community Medicine Department, Faculty of Medicine, University of Lampung, Indonesia*

MEDINFTech is licensed under a Creative Commons 4.0 International License.

ARTICLE HISTORY
Received: 17 June 24
Final Revision: 27 June 24
Accepted: 28 June 24
Online Publication: 30 June 24

KEYWORDS
Anti-fibrotic, Allogeneic, Bone Marrow Derived, Idiopathic Pulmonary Fibrosis, Mesenchymal Stem Cell, Renewable Therapy

CORRESPONDING AUTHOR
2218011098@students.unila.ac.id

DOI
10.37034/medinftech.v2i2.34

A B S T R A C T

Idiopathic pulmonary fibrosis (IPF) is a rare chronic respiratory disease characterized by progressive fibrotic changes in lung tissue of unknown origin, resulting in severe decline in lung function and poor prognosis with a median survival of 3 to 5 years. Current pharmacological therapies, including nintedanib and pirfenidone, aim to slow disease progression but are limited by side effects and lack of efficacy in reversing established fibrosis. This literature review explores emerging therapeutic approaches for IPF using data from PubMed, Google Scholar, and ScienceDirect databases. The review highlights mesenchymal stem cell (MSC) therapy, specifically allogeneic bone marrow-derived MSCs, as a promising option. MSC therapy demonstrates superior efficacy in improving forced vital capacity (FVC) by 3.7%, surpassing the effects of nintedanib (3.3%) and pirfenidone (-4.8%), while exhibiting minimal adverse effects. The findings underscore the potential of MSC therapy as a renewable treatment option for IPF, suggesting a paradigm shift towards addressing both disease progression and lung function restoration in affected individuals.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and irreversible respiratory disease characterized by the formation of progressive fibrotic tissue in the lung interstitium [1]. Globally, idiopathic pulmonary fibrosis is a rare disease with an ever-increasing prevalence. On the European and North American continents, the incidence of idiopathic pulmonary fibrosis is estimated to occur at 2.8 to 18 cases per 100.000 people each year, while on the Asia and South American continents, the incidence of idiopathic pulmonary fibrosis is estimated to occur at a lower number of cases, namely 0.5 to 4.2 cases per 100.000 people annually [2]. Even though it is a rare disease, idiopathic pulmonary fibrosis cannot be ignored. This disease has a poor prognosis of life expectancy ranging from 3 to 5 years in patients without therapy after the diagnosis [3].

In its management, patients with idiopathic pulmonary fibrosis can be given two types of therapy, namely pharmacological and non-pharmacological treatment. The pharmacological therapy can be carried out by prescribing two anti-fibrotic drugs, namely nintedanib and pirfenidone [4]. Based on the results of the latest clinical trials, these two drugs have been proven to slow down the progression of pulmonary fibrosis. However, in their use, there are still several shortcomings found, such as side effects on the gastrointestinal system and not having a curative effect on fibrotic tissue that has already formed [1]. Meanwhile, non-pharmacological therapy can be provided through prescribing oxygen therapy and lung transplant procedures [5]. As with pharmacological treatment, providing non-

pharmacological therapy also has several disadvantages, such as difficult access to therapy, a small number of lung organ donors, immune rejection, and complications of surgical procedures [1].

Based on the results of the analysis of various literature sources, it can be seen that there is a renewable cell-based therapy model for the management of idiopathic pulmonary fibrosis patients. This therapy utilizes the ability of stem cells or stem cells derived from the donor's body to create a secretome microenvironment that is useful in regeneration. This new therapeutic model works on the principle of improving lung function, which has previously decreased due to the formation of fibrotic tissue, especially lung function related to Forced Vital Capacity (FVC) and Diffusing Capacity of the Lung for Carbon Monoxide (DLCO). Indirectly, with an increase in lung function in the form of these two things, the survival rate of idiopathic pulmonary fibrosis patients will also increase [6]. Therefore, research on idiopathic pulmonary fibrosis management strategies that are safer and easier to implement is urgently needed.

2. Research Method

The review on the potential of Allogeneic Bone Marrow-derived Mesenchymal Stem Cells (BM-MSCs) as a renewable therapy for Idiopathic Pulmonary Fibrosis (IPF) spanned from April to June 2024. The search encompassed both Indonesian and English language articles sourced from reputable databases including PubMed, Google Scholar, and ScienceDirect. Keywords used in the search included "Idiopathic Pulmonary Fibrosis," "Mesenchymal Stem Cell," "BM-MSCs," "Clinical Trials," "Nintedanib," "Pirfenidone," and "Percentage Predicted FVC." The review utilized an analytical methodology involving systematic data collection, comprehensive information synthesis, logical argumentation, and the derivation of conclusions. A total of 18 pertinent articles were meticulously selected for inclusion based on their relevance to the topic.

3. Result and Discussion

3.1. Idiopathic Pulmonary Fibrosis

The lungs are an important organ of the respiratory system that facilitates the exchange of oxygen between the circulatory system and the body's external environment. Anatomically, the respiratory system is divided into 2 structures, namely the conductive and respiratory structures. Therefore, in the breathing process, 2 main stages occur, namely ventilation and perfusion. Ventilation is the entry of air from the body's external environment through the conductive structures of the respiratory system until it enters the alveoli. Meanwhile, perfusion is blood flow to the alveolar capillaries. The existence of these two stages will form a new stage called diffusion or the process of gas exchange between the external environment and gasses in the body's circulatory system [7].

In general, lung function can be determined through Forced Vital Capacity (FVC) and Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) tests. FVC is the maximum amount of air that can be expelled after taking the deepest possible breath, while DLCO is a measurement of the diffusion of gas exchange capacity of the lungs by paying attention to carbon monoxide levels [6]. Therefore, if there is disturbance or damage to the structure of the alveoli and blood capillaries, this will directly reduce the values of the two pulmonary function test parameters, namely FVC and DLCO. One disorder that can cause this is pulmonary fibrosis [7].

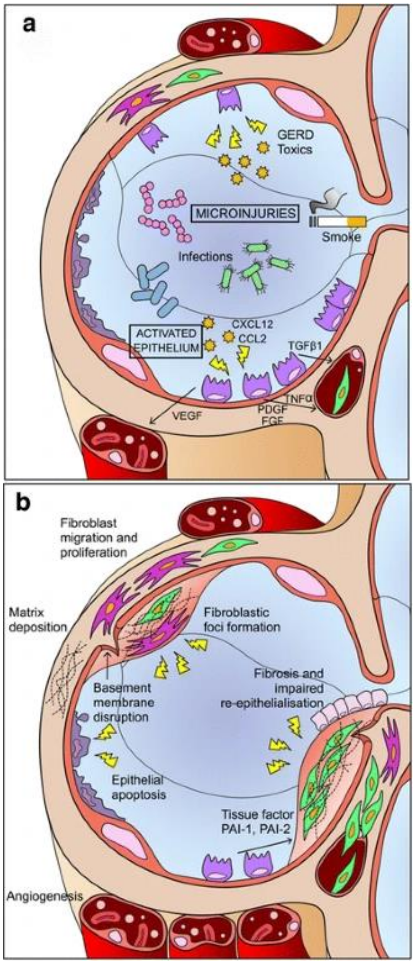

Figure 1. Idiopathic Pulmonary Fibrosis (IPF) Pathogenesis. Injuries repeated continuously causing maladaptive repair (a) and accumulation of myofibroblasts, fibroblasts, and epithelium afterwards (b) [21].

Figure 1 explains the pathogenesis of Idiopathic Pulmonary Fibrosis (IPF). Figure 1a illustrates the repeated injury process resulting in abnormal repair, while Figure 1b depicts the accumulation of myofibroblasts, fibroblasts, and epithelial cells in the subsequent process.

Pulmonary fibrosis is the process of fibrotic tissue forming in the lung parenchyma which can be caused by various factors. If after carrying out the examination and the causative factor is not found or is not known for certain, then the pulmonary fibrosis can be classified as idiopathic pulmonary fibrosis (IPF). On a CT scan, lungs with idiopathic fibrosis will show symptoms similar to usual interstitial pneumonia (UIP), namely the formation of honeycomb appearance opacities in the subpleural or basal region, bronchiectasis, and the formation of fibroblast foci. In general, the pathogenesis of IPF is caused by repeated alveolar micro injury which leads to dysfunction of the alveolar epithelium to regenerate. On the other hand, the presence of this dysfunction is also caused by several factors such as telomere shortening, aberrant mitochondrial bioenergetics, and increased endoplasmic reticulum stress caused by the unfolded protein response. Some of these things have the consequence of forming profibrotic mediators such as increasing the effects of transforming growth factor-β1 (TGF-β1), platelet-derived growth factor (PDGF), chemokine ligand 2 (CCL2), and chemokine (C-X-C motif) ligand 12 (CXCL12) [1].

IPF treatments that have been approved by the Food and Drug Administration are nintedanib and pirfenidone [8]. These two drugs have antifibrotic effects which can inhibit or reduce the formation of profibrotic cytokines so that they can reduce the degree of fibrosis activation and reduce the decrease in FVC in IPF patients [9]. However, both have side effects on the gastrointestinal system, such as diarrhea, nausea, and vomiting [10]. Therefore, renewable therapies are needed that have fewer side effects, but are still easily accessible and have good safety and effectiveness to treat IPF, such as mesenchymal stem cells (MSC) which have gone through phase I/IIa clinical trials so they are safe for further research.

3.2. Human Mesenchymal Stem Cell

Human mesenchymal stem cell (hMSC) is a somatic progenitor cell that has broad immunomodulatory properties [11]. The use of mesenchymal stem cells has been proven effective in improving lung function and increasing the survival phase of chronic inflammatory lung disease (asthma), chronic obstructive pulmonary disease (COPD), pulmonary hypertension, and idiopathic pulmonary fibrosis (IPF) [12]. Studies show that MSCs have various advantages such as diverse sources, easy availability, wide proliferative properties, minimal ethical issues, and low immunogenicity. In preclinical studies, MSCs show potential as a new treatment for lung diseases. MSCs contribute to tissue regeneration and remodeling, reduce chronic airway inflammation, and restore alveolar fluid balance in acute lung injury [13]. These properties make MSCs ideal candidates for tissue engineering, regenerative medicine, and cell-based therapies for IPF [14].

In the body system, MSCs are located in perivascular cells in vivo and when local injury occurs, MSCs will be activated and recruited to the injury site by releasing bioactive molecules that regulate the local immune response and form a microenvironment that promotes regeneration. MSCs work by encouraging epithelial tissue repair and have strong immunomodulatory properties which can be observed through direct cell-to-cell interactions or the secretion of bioactive products in the form of the secretome. This bioactive product consists of a series of molecules and extracellular vesicles that are useful for enhancing tissue repair effects. Some examples of bioactive products secreted by MSCs to support their function are VEGF which plays a role in proliferation and migration of endothelial cells, acceleration of angiogenesis, increasing fibroblast migration; PDGF which increases the proliferation, migration, and invasion ability of fibroblast cells and endothelial cells; KGF for accelerated proliferation and migration of keratinocyte cells in wound closure; IL-6 and IL-8 to increase wound angiogenesis and epithelial regeneration; EGF to increase fibroblast proliferation; TGFβ3 and TGFβ1 to promote extracellular matrix rearrangement, improve wound healing, and reduce scar formation; HGF for re-epithelialization, epidermal cell differentiation, fibrosis, and angiogenesis; and bFGF for fibroblast migration and proliferation [15]. On the other hand, an in vivo study in male wistar rats reported that the use of hMSCs was proven to work potently in reducing levels of TGF-β1, LOX, and TNF-α, as well as having a prophylactic effect against toxic CCl4 levels that cause lung fibrosis, collagen deposition, ROS formation, and cytokine production [16].

3.3. Comparison of Stem Cell Therapy and Antifibrotic Drugs

A 2019 investigation employing both in vitro and in vivo methodologies explored the influence of Nintedanib on pulmonary hypertension (PH). The study aimed to elucidate the mechanisms of action underlying this effect. Their findings demonstrated that Nintedanib improves hemodynamic parameters and attenuates vascular remodeling, manifested by reductions in neointimal lesions and medial wall thickening. These observations suggest Nintedanib possesses anti-vascular remodeling properties [23].

Nintedanib is a drug that works inside cells and blocks enzymes involved in cell signaling, including those for fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor. Studies in cells and animals have shown that nintedanib disrupts scarring processes, such as the growth, movement, and development of cells that produce scar tissue, and the production of the material that surrounds cells [22].

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridine) exerts its effects through modulation of tumor necrosis factor (TNF) and transforming growth factor-β (TGF-β)

signaling pathways. This results in the inhibition of fibroblast proliferation and collagen deposition, thereby accounting for its antifibrotic and anti-inflammatory properties [23]. The efficacy of these mechanisms has been confirmed in numerous in vitro and in vivo studies [24].

Furthermore, pirfenidone has demonstrated a statistically significant impact on slowing the decline of forced vital capacity (FVC), exceeding the effectiveness of other antifibrotic medications [25]. This compelling evidence led to its approval for the treatment of idiopathic pulmonary fibrosis (IPF) in Europe (2011) and the United States (2014) [23].

Based on the results of studies that have been carried out, a comparison between the results of antifibrotic drug therapy (nintedanib and pirfenidone) and administration of mesenchymal stem cells for idiopathic pulmonary fibrosis (IPF) can be observed through the results of changes in the patient's forced vital capacity (FVC%) values. Observations were made by reviewing the FVC value at week 52 (12th month) after therapy was given with the following results:

Table 1. Comparison of FVC% Improvement between Anti-fibrotic Drugs Therapy and Mesenchymal Stem Cell

Therapeutic Agent	Dose	Administration Interval	Clinical Trial Duration (weeks)	FVC (%)	Source
Allogeneic BM-derived MSC	200 x 10^6	Twice weekly	52	+3.7	[12]
Pirfenidone	2.403 mg	Once daily	52	-4.8	[18]
Nintedanib	150 mg	Twice daily	52	+3.3	[17]

Table 1 presents a comparison of the effects of different therapeutic agents on Forced Vital Capacity (FVC) improvement in patients with Idiopathic Pulmonary Fibrosis (IPF). Allogeneic Bone Marrow-derived Mesenchymal Stem Cells (BM-MSCs), administered at a dose of 200 million cells twice weekly over 52 weeks, showed a notable increase in FVC by +3.7% from baseline [12]. In contrast, patients treated with pirfenidone, given at 2,403 mg once daily for 52 weeks, experienced a decline in FVC by -4.8% [18]. Nintedanib therapy, administered at 150 mg twice daily over the same period, resulted in an improvement in FVC by +3.3% [17]. Based on these results, it can be seen that apart from being able to improve lung function as indicated by an increase in FVC from baseline after therapy, giving mesenchymal stem cells to IPF patients can provide the highest positive effect when compared to other therapies through administering the antifibrotic drugs nintedanib and pirfenidone. These findings underscore the potential of BM-MSC therapy, highlighting its superiority in enhancing lung function compared to conventional antifibrotic medications like pirfenidone and nintedanib in the context of IPF treatment.

On the other hand, apart from increasing the FVC value of the patient, assessment of the improvement in lung function in patients with IPF who were given mesenchymal stem cell therapy can also be observed through the Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) in units of % and 6-minute walk distance (6MWDT) tests in units of meters in %. When compared with placebo, patients who were given mesenchymal stem cell (MSC) therapy, especially those derived from bone marrow, had a slower decrease in DLCO test values accompanied by an increase in 6MWDT test values, where the change in DLCO test values in patients from baseline was only -5.1% compared to placebo (-12.9%). Meanwhile, the patient's 6MWDT test change value from baseline increased to +24.2% compared to placebo which decreased to -6.7% [12].

3.4. Allogeneic BM-derived Stem Cell

Based on the source, MSCs can be divided into MSCs which are derived from bone marrow, fat tissue (adipose), dental pulp, menstrual blood, placenta, amnion, umbilical cord blood, and Wharton's jelly. Among the various types of MSCs, MSCs isolated from bone marrow are the MSCs that have the highest immunomodulatory activity and are most often used to treat lung diseases. When compared with adipose MSC, MSCs derived from the bone marrow can suppress CD4 and CD8 expression simultaneously, while MSCs derived from adipose can only suppress CD4 expression. This makes bone marrow-derived MSCs the best cell source for immune regulation [1]. In addition to safety data from preclinical studies, human trials have also demonstrated the safety and tolerability of IV allogeneic mesenchymal stem cells. The results of allogeneic bone marrow-derived MSC trials in intravenous IPF patients reported that no serious side effects occurred. On the other hand, at 60 weeks post-infusion, there was a mean decrease of 3.0% in predicted FVC and a 5.4% mean decrease in predicted lung diffusion capacity for carbon monoxide [19]. The side effects of using bone marrow-derived MSCs for idiopathic pulmonary fibrosis patients are considered to be lower. Based on clinical trials that have been carried out, it can be seen that the side effects that appear after patients are given MSC infusion are fever and chills with mild reactions so that there is no need to stop the study. However, on the other hand, side effects in the form of ischemic stroke were also found in one of the patients even though they improved after being given anticoagulant and vascular therapy [12]. However, there are still problems encountered in administering MSCs, especially those derived from bone marrow, such as small sample size, lack of randomization, lack of a

placebo group, the absence of determining the optimal number of infusions and appropriate dosing intervals, also the possibility of an immune rejection response and the lack of optimal development of delivery methods [12],[20].

4. Conclusion

The use of mesenchymal stem cells (MSC), especially those derived from bone marrow (BM), for idiopathic pulmonary fibrosis has been proven to have better therapeutic potential compared to current anti-fibrotic drugs. This is proven by the latest clinical trials which show that administered MSCs to idiopathic pulmonary fibrosis patients can increase FVC values by 3.7%, higher than nintedanib (3.3%) and pirfenidone (-4.8%) as first-line anti-fibrotic drugs accompanied by minimal side effects. However, the use of Allogeneic BM-derived MSCs as a renewable therapy still has several shortcomings such as small sample size, lack of randomization, lack of a placebo group, the absence of determining the optimal number of infusion and appropriate dosing intervals, also the possibility of an immune rejection response and the lack of optimal development of delivery methods. Therefore, further clinical research is needed, especially carefully designed phase II/III clinical study to evaluate the efficacy of allogeneic BM-derived MSCs as a renewable curative therapeutic modality in idiopathic pulmonary fibrosis, including combination studies with anti-fibrotic drugs so as to increase the life expectancy of patients with idiopathic pulmonary fibrosis.

References

[1] S. Yang, P. Liu, Y. Jiang, Z. Wang, H. Dai, and C. Wang, "Therapeutic applications of mesenchymal stem cells in idiopathic pulmonary fibrosis," *Frontiers in Cell and Developmental Biology*, vol. 9, Mar. 2021, doi: 10.3389/fcell.2021.639657.

[2] L. Richeldi *et al.*, "Long-term treatment of patients with idiopathic pulmonary fibrosis with nintedanib: results from the TOMORROW trial and its open-label extension," *Thorax*, vol. 73, no. 6, pp. 581–583, Oct. 2017, doi: 10.1136/thoraxjnl-2016-209701.

[3] F. Luppi, M. Kalluri, P. Faverio, M. Kreuter, and G. Ferrara, "Idiopathic pulmonary fibrosis beyond the lung: understanding disease mechanisms to improve diagnosis and management," *Respiratory Research*, vol. 22, no. 1, Apr. 2021, doi: 10.1186/s12931-021-01711-1.

[4] T. M. Dempsey, S. Payne, L. Sangaralingham, X. Yao, N. D. Shah, and A. H. Limper, "Adoption of the Antifibrotic Medications Pirfenidone and Nintedanib for Patients with Idiopathic Pulmonary Fibrosis," *Annals of the American Thoracic Society*, vol. 18, no. 7, pp. 1121–1128, Jul. 2021, doi: 10.1513/annalsats.202007-901oc.

[5] P. Millan-Billi, C. Serra, A. A. Leon, and D. Castillo, "Comorbidities, Complications and Non-Pharmacologic treatment in idiopathic pulmonary fibrosis," *Medical Sciences*, vol. 6, no. 3, p. 59, Jul. 2018, doi: 10.3390/medsci6030059.

[6] D. O. Ria, S. Suradi, J. Aphridasari, R. Reviono, and D. Indarto, "The Test of DLCO Is A Valuable Predictor for Prognostic Determination of Patients with Chronic Obstructive Pulmonary Disease," *Jurnal Respirologi Indonesia*, vol. 38, no. 2, pp. 83–92, Apr. 2018, doi: 10.36497/jri.v38i2.162.

[7] K. A. Powers and A. S. Dhamoon, "Physiology, pulmonary ventilation and perfusion," *StatPearls - NCBI Bookshelf*, Jan. 23, 2023. https://www.ncbi.nlm.nih.gov/books/NBK539907/

[8] R. Deterding *et al.*, "Study design of a randomised, placebo-controlled trial of nintedanib in children and adolescents with fibrosing interstitial lung disease," *ERJ Open Research*, vol. 7, no. 2, pp. 00805–02020, Mar. 2021, doi: 10.1183/23120541.00805-2020.

[9] V. Hadda and R. Guleria, "Antifibrotic drugs for idiopathic pulmonary fibrosis: What we should know?," *Indian Journal of Medical Research*, vol. 152, no. 3, p. 177, Jan. 2020, doi: 10.4103/ijmr.ijmr_90_20.

[10] M. Chianese *et al.*, "Pirfenidone and nintedanib in pulmonary fibrosis: Lights and Shadows," *Pharmaceuticals*, vol. 17, no. 6, p. 709, May 2024, doi: 10.3390/ph17060709.

[11] B. L. Yen, M. L. Yen, L. T. Wang, K. J. Liu, and H. K. Sytwu, "Current status of mesenchymal stem cell therapy for immune/inflammatory lung disorders: Gleaning insights for possible use in COVID-19," *Stem Cells Translational Medicine*, vol. 9, no. 10, pp. 1163–1173, Jun. 2020, doi: 10.1002/sctm.20-0186.

[12] A. Averyanov *et al.*, "First-in-human high-cumulative-dose stem cell therapy in idiopathic pulmonary fibrosis with rapid lung function decline," *Stem Cells Translational Medicine*, vol. 9, no. 1, pp. 6–16, Oct. 2019, doi: 10.1002/sctm.19-0037.

[13] M. Najar *et al.*, "Mesenchymal Stromal Cell-Based Therapy: New Perspectives and Challenges," *Journal of Clinical Medicine*, vol. 8, no. 5, p. 626, May 2019, doi: 10.3390/jcm8050626.

[14] Q. Lu and A. H. K. El-Hashash, "Cell-based therapy for idiopathic pulmonary fibrosis," *Stem Cell Investigation*, vol. 6, p. 22, Aug. 2019, doi: 10.21037/sci.2019.06.09.

[15] A. Ajit and I. A. Gopalankutty, "Adipose-derived stem cell secretome as a cell-free product for cutaneous wound healing," *3 Biotech*, vol. 11, no. 9, Aug. 2021, doi: 10.1007/s13205-021-02958-7.

[16] M. Khajvand-Abedini *et al.*, "The Restoring Effect of Human Umbilical Cord-Derived Mesenchymal Cell-Conditioned Medium (hMSC-CM) against Carbon Tetrachloride-Induced Pulmonary Fibrosis in Male Wistar Rats," *International Journal of Inflammation*, vol. 2022, pp. 1–10, Dec. 2022, doi: 10.1155/2022/7179766.

[17] K. R. Flaherty *et al.*, "Safety of nintedanib added to pirfenidone treatment for idiopathic pulmonary fibrosis," *European Respiratory Journal*, vol. 52, no. 2, p. 1800230, June. 2018, doi: 10.1183/13993003.00230-2018.

[18] S. D. Nathan *et al.*, "Pirfenidone in patients with idiopathic pulmonary fibrosis and more advanced lung function impairment," *Respiratory Medicine*, vol. 153, pp. 44–51, Jul. 2019, doi: 10.1016/j.rmed.2019.04.016.

[19] M. K. Glassberg *et al.*, "Allogeneic human mesenchymal stem cells in patients with idiopathic pulmonary fibrosis via intravenous delivery (AETHER)," *Chest*, vol. 151, no. 5, pp. 971–981, May 2017, doi: 10.1016/j.chest.2016.10.061.

[20] K. Kim, S. Bou-Ghannam, S. Kameishi, M. Oka, D. W. Grainger, and T. Okano, "Allogeneic mesenchymal stem cell sheet therapy: A new frontier in drug delivery systems," *Journal of Controlled Release*, vol. 330, pp. 696–704, Feb. 2021, doi: 10.1016/j.jconrel.2020.12.028

[21] G. Sgalla, B. Iovene, M. Calvello, M. Ori, F. Varone, and L. Richeldi, "Idiopathic pulmonary fibrosis: pathogenesis and

management," *Respiratory Research*, vol. 19, no. 1, Feb. 2018, doi: 10.1186/s12931-018-0730-2.

[22] Costabel U, Inoue Y, Richeldi L, Collard HR, Tschoepe I, Stowasser S, Azuma A. Efficacy of nintedanib in idiopathic pulmonary fibrosis across prespecified subgroups in INPULSIS. American journal of respiratory and critical care medicine. 2016 Jan 15;193(2):178-85.

[23] Chianese M, Screm G, Salton F, Confalonieri P, Trotta L, Barbieri M, Ruggero L, Mari M, Reccardini N, Geri P, Hughes M. Pirfenidone and Nintedanib in Pulmonary Fibrosis: Lights and Shadows. Pharmaceuticals. 2024 May 30;17(6):709.

[24] P. V. Shah, P. Balani, A. R. Lopez, C. M. N. Nobleza, M. Siddiqui, and S. Khan, "A review of pirfenidone as an Anti-Fibrotic in idiopathic pulmonary fibrosis and its probable role in other diseases," *Curēus*, Jan. 2021, doi: 10.7759/cureus.12482.

[25] L. Vietri *et al.*, "Pirfenidone in idiopathic pulmonary fibrosis: real-life experience in the referral centre of Siena," *Therapeutic Advances in Respiratory Disease*, vol. 14, p. 175346662090632, Jan. 2020, doi: 10.1177/1753466620906326.