

A Review on Novel Therapeutic Strategies in Respiratory System Disorders

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ABSTRACT:

Respiratory system disorders pose a significant global health challenge, substantially impacting morbidity, mortality, and healthcare burdens. Millions of people around the world have chronic respiratory diseases like asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease, pneumoconiosis, and pulmonary sarcoidosis. The rising incidence of these conditions underscores the necessity for enhanced therapeutic strategies that can efficiently alleviate symptoms, decelerate disease progression, and improve patient quality of life. This article examines novel and sophisticated therapeutic strategies for the treatment of respiratory system disorders. Standard treatments like bronchodilators, corticosteroids, and antibiotics can help with symptoms, but they often don't work well in the long term and can have side effects. Recent studies have concentrated on novel approaches, including targeted drug delivery systems, inhalation therapies, nanomedicine, and biological agents designed to enhance drug bioavailability and therapeutic efficacy. Inhalation devices, including nebulizers, metered-dose inhalers, and dry powder inhalers, have notably enhanced pulmonary drug delivery by facilitating localized treatment while minimizing systemic side effects. Advances in molecular pharmacology and biotechnology have also made it possible to create personalized medicine and treatments for specific diseases. These new treatments could make a big difference in how diseases are treated and how well patients do. In general, combining new drug delivery technologies with targeted therapeutic approaches is a promising way to treat respiratory system disorders in the future.

KEYWORDS: COPD, Asthma, Nanotechnology, Novel Therapies, Biologic Drugs

I. INTRODUCTION:

A wide range of pulmonary disorders are included in the category of chronic respiratory diseases (CRDs), such as pulmonary sarcoidosis (PS), asthma, pneumoconiosis, interstitial lung disease (ILD), and chronic obstructive pulmonary disease (COPD). Following cardiovascular illnesses, infections of the airways, TB, and neoplasms, CRDs are the fourth most common cause of death worldwide and contribute significantly to the total disease burden [1,2,3]. Conditions affecting the lungs and airways, such as asthma, pneumoconiosis, interstitial lung disease (ILD), pulmonary sarcoidosis, and chronic obstructive pulmonary disease (COPD), are together referred to as chronic respiratory diseases (CRDs). As the third most common cause of death worldwide in 2019, CRD is linked to a significant burden and expense [4,5,6]. The detailed epidemiological data provided by the Global Burden of Disease (GBD) studies has been essential in directing research priorities and influencing health policy [7]. According to the World Health Organization, lower respiratory infections (LRIs) are the most deadly infectious illness, ranking as the fourth most prevalent cause of death globally in 2019. Additionally, according to a recent Global Burden of Disease (GBD) research, there were around 488.9 million lower respiratory infection incident cases in 2019, and 2.4 million people died as a result [8]. *Streptococcus pneumoniae*, *Haemophilus influenzae*, influenza viruses, respiratory syncytial virus, and other common pathogens are among the frequent bacteria that cause LRIs, a common kind of respiratory illness [9]. A recent GBD research from 2019 found that the third-largest risk factor for LRIs worldwide was a lack of handwashing facilities, which accounted for 14.4% of the burden [8]. Globally, upper respiratory infections (URIs) constitute the primary cause of acute illness occurrence [10]. URIs can be contracted by a number of respiratory pathways, including as inhaling aerosols from an infected person or transferring bacteria onto mucous

membranes through contaminated hands [11,12]. Rhino viruses, coronaviruses, influenza, respiratory syncytial virus (RSV), Streptococcus pyogenes, Streptococcus pneumoniae, Haemophilus influenzae, and Mycoplasma pneumoniae are among the many microorganisms that cause upper respiratory infections (URIs). Given the vast number of URI cases that occur each year, there is a significant chance that URIs may develop into more serious illnesses. In the wake of the COVID-19 pandemic, which frequently resulted in infections starting in the upper respiratory tract before developing into more serious illnesses, this possible danger is especially significant [13,14]. Inhalers are the mainstay of therapy for asthma and COPD. Over 30% of persons with asthma have poor inhalation technique, which results in 80% of the drug being deposited in the oropharynx. This raises the possibility of systemic or local side effects and drastically changes the effectiveness of treatment [15].

II. OVERVIEW OF RESPIRATORY SYSTEM DISORDERS:

Millions of people worldwide suffer with asthma, a common chronic inflammatory respiratory disease that can be difficult to diagnose and treat. Inflammation of the airways, which results in sporadic airflow restriction and bronchial hyperresponsiveness, is the hallmark of this respiratory illness. Coughing, wheezing, and shortness of breath are the classic symptoms of asthma, and they are often made worse by triggers that range from viral infections to allergens. A complicated interaction between environmental and genetic variables determines the incidence and severity of asthma. Disparities in asthma care still exist despite improvements in therapy, with various demographic groups having uneven access to diagnosis, treatment, and patient education. Other atopic characteristics including hay fever and eczema are linked to the development of asthma, which frequently manifests in infancy [16,17,18]. It is estimated that 260 million people globally suffer from asthma [19]. The prevalent and curable condition known as chronic obstructive pulmonary disease (COPD) is typified by tissue damage and increasing airflow restriction. Chronic inflammation brought on by extended exposure to harmful particles or gases—most frequently cigarette smoke—is linked to structural alterations in the lungs. Lung recoil is reduced and airways shrink as a result of chronic inflammation. The illness frequently manifests as coughing, dyspnea, and

sputum production. From respiratory failure to a lack of symptoms, symptoms might vary [20]. Laennec first characterized bronchiectasis in the beginning of the nineteenth century. Because of recurrent infections that lead to bacterial invasion and mucus pooling throughout the bronchial tree, bronchiectasis is a chronic lung illness marked by a lifelong and continuous enlargement of the bronchial airways and a weakening of the mucociliary transport system [21,22,23]. The chronic, progressive lung condition known as pulmonary fibrosis (PF) is characterized by an excessive buildup of extracellular matrix (ECM) components, which causes lung tissue scarring and restricted respiratory function [24]. Prolonged dyspnea, coughing, hypoxia, decreased lung function, diffuse bilateral infiltrates on imaging, inflammation, fibrosis, restricted patient mobility, and a worse quality of life (QOL) are all signs of ILD [25]. Although the exact pathophysiological causes are unknown, ILD is classified as a restrictive lung disease that lowers total lung capacity (TLC) and lung expansion [26]. Mycobacterium tuberculosis (M. tb), another name for the tubercle bacillus, was discovered by Robert Koch in 1882 and is the causative agent of tuberculosis (TB) [27]. Seasonal influenza A and B viruses, which are spread around the world, invade the respiratory system and produce influenza, an acute viral respiratory illness. The topic of this seminar is seasonal influenza, which is defined as illness in humans brought on by infection with seasonal influenza A or B viruses. In temperate locations across the world, annual influenza outbreaks of varying intensity usually happen during winter months. In tropical and subtropical regions, influenza activity is year-round and peaks at different periods [28].

CURRENT PHARMACOTHERAPEUTIC MANAGEMENT (CONVENTIONAL APPROACH) MAJOR DRUG CLASSES:

BETA-2 AGONISTS:

Transmembrane glycoproteins called beta (β)-adrenergic receptors bind to catecholamines and cause intracellular reactions. They particularly associate with guanine nucleotide (GTP)-binding proteins (G proteins) and are members of the G-protein-coupled receptor (GPCR) family, also referred to as R7G [29].

Beta-2 Adrenergic Receptor Agonists

Drugs that specifically activate β_2 adrenergic receptors are known as β_2 adrenergic receptor agonists. Though their action is mostly limited to β_2 receptors, these receptors are categorized as sympathomimetics and imitate the effects of endogenous catecholamines like norepinephrine and adrenaline. They are mostly utilized in clinical settings because of their specific effects on the smooth muscle of the airways, which lead to bronchodilation and relaxation [30,31].

SHORT ACTING BETA-2 AGONIST:

Albuterol (also called salbutamol), levalbuterol, metaproterenol, and terbutaline are examples of short-acting β_2 agonists (SABAs) that are mainly administered to treat acute bronchospasm brought on by diseases including asthma and chronic obstructive pulmonary disease (COPD). They can be used to relieve acute symptoms because of their quick onset and brief duration of effect [32,33].

LONG ACTING BETA-2 AGONIST:

Salmeterol, formoterol, and arformoterol are examples of long-acting β_2 agonists (LABAs) that are recommended for the maintenance treatment of bronchoconstriction in patients with emphysema, COPD, asthma, and chronic bronchitis. When combined with inhaled corticosteroids, several LABAs, especially formoterol, can also be used to treat acute asthma [34].

ANTICHOLINERGICS:

The term "anticholinergics" refers to medicines that prevent and reduce the action of the neurotransmitter acetylcholine (ACh) at synapses in the central and peripheral nervous systems [35]. The FDA has authorized the use of ipratropium and tiotropium among individuals with chronic obstructive pulmonary disease because they widen the airways and reduce dyspnea [36].

CORTICOSTEROIDS:

Since their invention, corticosteroids have been employed by practically every method and in almost every branch of medicine [37]. Glucocorticoids and mineralocorticoids are examples of corticosteroids, which are artificial analogues of the natural steroid hormones generated by the adrenal cortex. The synthetic hormones exhibit a range of mineralocorticoid and

glucocorticoid characteristics. Glucocorticoids have vasoconstrictive, anti-inflammatory, and immunosuppressive properties and are primarily engaged in metabolism. On the other hand, mineralocorticoids influence ion transport in the renal tubules' epithelial cells, which controls electrolytes and water balance [38].

METHYLYXANTHINES:

Caffeine, paraxanthine, theobromine, and theophylline are all members of the family of hallucinogenic purine alkaloids known as methylxanthines [39,40]. For severe flare-ups of chronic obstructive pulmonary disease (COPD), the Global Approach for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease (GOLD) guidelines currently suggest adding an oral or intravenous methylxanthine to aerosolized bronchodilators [41]. Individuals with stable COPD may benefit from the effects of methylxanthines, which include bronchodilation, immunomodulation, as well as broncho-protection [42,43].

MUCOLYTICS AND EXPECTORANTS:

Mucolytics increase mucociliary clearance and encourage sputum expectoration by controlling the viscoelastic characteristics of mucus, primarily by modifying the degree of crosslinks and molecular interactions within mucin polymers [44]. Clinically available expectorant medications work to improve mucociliary clearance, decrease mucus viscoelasticity, restore the natural structure and function of the mucus layer, suppress mucin formation and secretion, and speed up mucus transport. They are therefore referred to as mucoactive agents [45,46].

NOVAL THERAPEUTIC STRATEGIES: CLASSIFICATION AND CONCEPT:

Novel therapeutic strategies denote treatment methodologies derived from advancing scientific insights, as opposed to conventional symptom-oriented care. A therapy is deemed "novel" if it presents new molecular targets, groundbreaking delivery systems, or tailored interventions grounded in disease mechanisms. The current trend focuses on a mechanistic framework, in which treatments are made to change certain biological pathways that cause diseases to get worse. This is a clear shift from traditional symptomatic management to treatment that is based on precision and targets. These strategies aim to improve drug development by aligning it with

pathophysiology. They also aim to improve efficacy, reduce side effects, and support personalized healthcare models that reflect progress in pharmacology and translational medicine.

NOVAL DRUG TARGETS AND NEW PHARMACOLOGICAL AGENTS:

PDE INHIBITORS:

The primary organ of the respiratory system, the lungs, expand and contract over a thousand times a day to facilitate effective gas exchange. Chronic respiratory disorders are conditions or pathologies of the lungs and airways that progress gradually and get worse over time [47]. An enzyme called phosphodiesterase (PDE) is implicated in the pathophysiology of a number of degenerative and chronic inflammatory disorders in humans [48]. PDE inhibitors are a significant family of medications that are presently being studied as a therapeutic approach for fragile X syndrome, atopic dermatitis, depression, asthma, COPD, and cognitive and emotional problems [49]. But the only PDE4 inhibitor that is presently authorized for the management of respiratory conditions is roflumilast, which is used as a second-line drug for severe COPD with chronic bronchitis [48]. Patients with severe COPD linked to chronic bronchitis and a history of exacerbations should be treated with roflumilast, a strong and specific inhibitor of phosphodiesterase-4 (PDE4) [50,51]. Cyclic adenosine monophosphate (cAMP) hydrolysis in inflammatory cells is inhibited by selective PDE4 inhibition [52]. Numerous anti-inflammatory actions are produced by increased intracellular cAMP, such as reduced neutrophil production of inflammatory mediators and cytokine release [51]. Patients with COPD exacerbations, who frequently have higher inflammatory markers than patients with baseline illness, typically benefit from the inhibition of inflammatory mediators and cytokines [53]. Additionally, roflumilast inhibits inflammation brought on by allergens [54]. It has been demonstrated to reduce systemic inflammation brought on by lipopolysaccharide [55].

PROTEASE INHIBITORS:

One of the primary physiological processes thought to be engaged in the pathophysiology of COPD is the protease:antiprotease imbalance [56]. A1AT deficiency is one of the primary genetic causes of COPD [57]. The main regulator of NE activity is thought to be A1AT. About 90% of the anti-NE action in the lower respiratory tract in

healthy lungs is attributed to A1AT, which shields the underlying connective tissues [58]. Proteinase 3, cathepsin G, neutrophil serine protease 4, and NE are the four forms of serine proteases found in neutrophils, with NE being the most prevalent [59]. Mature neutrophils deposit NE in their azurophilic granules. It has a molecular weight of 29.5 kDa and 218 residues [60]. Sivelestat is a selective NE inhibitor that helps with a number of systemic and pulmonary disorders. It can mitigate alveolar epithelial and vascular endothelial damage and lessen the symptoms of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) by reversing neutrophil-mediated increases in vascular permeability [61]. A new selective NE inhibitor that may be used orally is called AZD9668. Oral AZD9668 (60 mg twice daily for 4 weeks) was found to enhance lung function and lower sputum inflammatory biomarker levels when compared to a placebo in a phase II clinical study including BE patients [62]. A new selective NE inhibitor that is inhaled is called POL6014. Research has shown that after a single dosage, inhaled POL6014 can safely reach high lung concentrations and dramatically reduce NE in CF patients' sputum [63].

ANTI-INFLAMMATORY OR IMMUNOMODULATORY TARGETS:

IL-5, a Th2 cell cytokine, is crucial for the maturation, differentiation, recruitment, and survival of eosinophils. In asthma models where eosinophilia and AHR are significantly decreased, IL-5 knockout mice seemed to indicate a role. Mepolizumab (formerly known as SCH55700) and reslizumab (previously known as Res-5-0010) are humanized anti-IL-5 monoclonal antibodies (MAbs) that have been developed for clinical application [64]. Benralizumab, a different completely humanized MAb that was formerly known as MEDI-563, targets eosinophils by binding IL-5 receptor α (IL-5R α), blocking IL-5 binding, and causing eosinophil death via antibody-dependent cell-mediated cytotoxicity [65]. Goblet cell metaplasia and epithelial-mesenchymal signaling are two features of airway inflammation and epithelial remodeling in which IL-13 has been demonstrated to be crucial as part of the Th2 theory of asthma. Increased subepithelial fibrosis or airway smooth muscle hyperplasia result from this [66].

BIOLOGICS AND MONOCLONAL ANTIBODIES IN RESPIRATORY DISEASE: BIOLOGICS IN ASTHMA:

The first biologic treatment for asthma was omalizumab, which was officially licensed in 2003 for severe asthma. Omalizumab is a monoclonal antibody that inhibits degranulation by specifically targeting IgE and blocking its attachment to mast cells and basophils. Omalizumab is therefore especially helpful for people who have atopic asthma. However, it is not appropriate for usage during asthma flare-ups since it does not directly interact with the effector cells [67]. Mepolizumab is a monoclonal antibody that has a high affinity for IL-5 and inhibits both the cascade of eosinophilic airway inflammation and the link to its receptor. Patients with severe asthma who are six years of age or older and have serum eosinophils more than 150/ μ L are eligible for mepolizumab. Even in individuals who have an indication for omalizumab or who are uncontrolled despite taking omalizumab, mepolizumab appears to be successful [68]. In contrast to mepolizumab, reslizumab is an injectable monoclonal antibody that also targets IL-5. Patients with severe asthma and serum eosinophil counts more than 400/ μ L who are at least 18 years old are eligible for reslizumab [69]. Every four weeks, a weight-adjusted intravenous dosage of reslizumab is given. The most frequent side effects of reslizumab include autoantibody formation (<5%), early- or late-stage anaphylaxis (<1%), and a brief increase in creatinine phosphokinase (up to 20%) [70]. Benralizumab is a monoclonal antibody that specifically targets the IL-5 receptor. By preventing IL-5 from binding to its receptor on eosinophils and basophils, it restricts the recruitment, differentiation, maturation, and activation of those cells. Additionally, benralizumab promotes pro-apoptotic cytokines that are known to induce eosinophil apoptosis by targeting the receptors of neutrophils, macrophages, and natural killer cells [69].

BIOLOGICS IN COPD AND OTHER CONDITIONS:

Clinical trials and real-world investigations have shown that benralizumab, a monoclonal antibody that targets the α -subunit of the IL5 receptor of eosinophils and basophils, is effective in treating severe asthma with T2 inflammation. The effectiveness of benralizumab at a dose of 100 mcg in COPD was evaluated in a phase II study involving 101 patients with sputum eosinophil counts above 3%. While reductions in sputum and peripheral blood eosinophil counts were noted, there

were no discernible differences in the reduction of exacerbations [71]. Tezepelumab, an anti-TSLP newly licensed for severe asthma, is one among them and is being researched in patients with COPD. Patients with moderate to severe COPD who experience frequent exacerbations while taking triple inhaled treatment are included in the COURSE trial (NCT04039113), a phase 2a research using tezepelumab or placebo. With 12 registered studies, other biologics that inhibit IL33 (itepekimab, tozorakimab) or its ST2 receptor (astegolimab) show great potential for treating COPD in the future [72].

STEM CELL THERAPY AND REGENERATIVE APPROACHES:

All immune cells involved in the pathophysiology of inflammatory lung diseases, such as neutrophils, effector and regulatory T cells, and professional antigen-presenting cells (dendritic cells (DCs), macrophages, and B lymphocytes), can have their proliferation, activation, and effector function modulated by MSCs. MSCs use juxtacrine or paracrine pathways to modify the immune response [73]. In vitro, MSCs can inhibit CD4+Th2 cell growth and effector function, plasma cell IgE synthesis, and IgE-dependent mast cell activation [74]. According to these results, a number of studies showed that MSCs might reduce airway remodeling and inflammation while also enhancing lung function in mice with asthma [75,76,77,78]. The administration of BM-MSCs and AT-MSCs (in a minimum of 5×10^4 cells/animal) intravenously, intratracheally, and intrabronchially was a safe therapeutic approach that demonstrated positive effects in both structural and functional outcomes in the COPD animal models, which were prepared either by elastase instillation or by cigarette smoke exposure [79]. Even better than lung tissue-derived MSCs (LT-MSCs), the greatest results were observed following intratracheal injection of BM-MSCs. It's interesting to note that intravenous injection of LT-MSCs caused the recipient mice to die instantly; this was not the case when BM-MSC or AT-MSCs were administered intravenously [80]. Exocytosis produces a kind of membrane vesicles called exosomes, which range in diameter from 30 to 100 nm. Numerous cells, including B lymphocytes, dendritic cells, mast cells, platelets, and several tumor cells, can release it [81]. Exosomes function in the following three ways: 1. The target cells get the enzymes or RNAs from the exosomes once they are taken up by the recipient cells via endocytosis; 2. The target cells' activity is

changed when the ligands on the exosomes attach to the matching receptors on the surface of receiving cells, activating the downstream signal pathway [82]. Lung regenerative medicine has advanced in a number of ways, including stem cells and cells. The ability of stem cells to differentiate into several cells and create tissue regeneration, tissue homeostasis, and growth is known as multipotent capability. Co-cultured cells and corporate stem cells can produce complex tissues and organs [83]. Stem cells have been employed as seed cells in several research recently. When integrating biomaterials, co-culture, gene delivery, or cytokines to enhance tissue development, stem cell culture may more accurately replicate the microenvironment in vivo thanks to 3D culture and the utilization of bioreactors. Furthermore, in situ tissue regeneration methods can provide a tissue for in vivo engineering [84].

NANOTECHNOLOGY AND TARGETED DRUG DELIVERY SYSTEMS: NANOCARRIERS:

After being breathed, NPs can diffuse throughout the respiratory system and land in the alveoli, where they can interact with pulmonary surfactant (PS) and epithelial cells [85]. Pharmacology is significantly impacted by the use of liposomes as a medication delivery mechanism. Phospholipids and cholesterol make up the majority of liposomes, a kind of lipid vesicles. A self-assembling lipid bilayer with amphiphilic domains, including an outer shell of the lipid bilayer and an interior watery core, makes up this colloidal form [86]. Another kind of lipid-based substance that differs somewhat in structure from liposomes is SLNs. Due to their many benefits—such as targeted drug delivery, controlled release, high drug stability, high drug loading, encapsulation of hydrophilic and lipophilic drugs, low carrier toxicity, avoidance of organic solvents in production (such as high-

pressure homogenization), and large-scale industrial production—SLNs may be a viable substitute for conventional carrier systems [87,88]. One kind of giant molecule chemical complex made up of many smaller homogenous molecules is called a polymer. Albumin, gelatin, alginate, collagen, cyclodextrin, and chitosan are examples of natural polymers; poly-lactic-co-glycolic acid (PLGA), polyacrylates, polyethyleneimine (PEI), PEG, polyanhydrides, and poly-l-lysine are examples of synthetic polymers [89]. One kind of polymer nanostructure that differs from conventional polymers is a dendrimer. Its three-dimensional structure is monodisperse and extremely branching. A dendrimer's flexibility and biocompatibility as a nanocarrier are enhanced by the many functional groups dispersed over its surface [90].

INHALABLE NANOFORMULATIONS:

MDIs Drug-containing liquids, emulsions, or suspensions are encased in pressure-resistant containers with particular valves and an appropriate propellant in MDIs, a form of inhalation device that is currently widely utilized in clinical practice. An aerosol is created and released using the energy from the propellant ejection [91,92].

DPIs: To solve the issue of actuation and inhalation coordination, DPIs are powdered drug-containing particles of propellant-free formulations that are forced into the airway by the patient's inhaling airflow. DPIs are made in the form of dry powder or solid micronized APIs, either by themselves or in conjunction with appropriate carriers. These are then put into a particular device in the form of blisters, capsules, or multi-dose reservoirs. There are three varieties of DPIs: single-dose, multi-unit dosage, and multi-dose. Drug deposition rates in the lungs vary widely amongst products, usually ranging from 12 to 40% [93,94,95,96].



Nebulizer



Metered Dose Inhaler



Dry Powder Inhaler

NEBULIZERS: Nebulizers are devices that give energy to transform a drug-containing solution or suspension into an aerosol that may be breathed through a mask using compressed gas (air or oxygen), ultrasound, and electric shock. Jet nebulizers, ultrasonic nebulizers, and vibrating mesh nebulizers are the three primary varieties [93,97].

EMERGING THERAPIES IN PULMONARY FIBROSIS AND ILDs: PDE4B INHIBITION:

A common intracellular second messenger, cyclic adenosine monophosphate (cAMP) is essential for the operation of several organs, including the lung, the central nervous system, immunology and inflammation, and the endocrine system. Phosphodiesterases, especially the cAMP-specific phosphodiesterase-4 (PDE4) family, tightly control cellular cAMP levels by selectively hydrolyzing cAMP, which in turn affects the activity of downstream effectors like protein kinase A (PKA), exchange proteins directly activated by cAMP (EPAC), and Popeye domain-containing proteins [98]. PDE4 enzymes function as important regulators of fibrotic and inflammatory signaling pathways via various methods [99]. Oral preferred phosphodiesterase-4B (PDE4B) inhibitors include nerandomilast. Nerandomilast modulates many inflammatory and profibrotic signaling pathways by raising intracellular cAMP concentrations through PDE4B inhibition [100].

TGF- β Inhibition with Inhaled Pirfenidone and Structural Analogues:

Over the course of a maximum 72-week treatment duration, participants were randomly assigned to receive nebulized AP01 at either 50 mg once day (QD) or 100 mg twice daily (BID) via a portable nebulizer. With a mean drop in percent predicted FVC of just -0.4% (about -34 mL) after 48 weeks, the higher-dose group (100 mg BID) showed remarkable stability in lung function, while the 50 mg QD group had a decline of -4.9% (about -188 mL). Inhaled pirfenidone showed a favorable safety and tolerability profile in addition to maintaining lung function. There was a significant decrease in the frequency of systemic adverse effects that are frequently observed with oral pirfenidone, including nausea, dyspepsia, rash, and weight loss. The majority of adverse effects were modest, with cough and throat discomfort associated with the inhalation method being the most common. Significantly, a low percentage of treatment termination owing to adverse events suggests that

inhaled delivery may enhance long-term adherence. The AP01-005 extension research, which included both IPF and non-IPF fibrosing ILD patients, also investigated long-term safety and effectiveness. A portion of participants in this open-label follow-up continued to take inhaled pirfenidone for a maximum of 240 weeks. These individuals showed no signs of cumulative toxicity and maintained steady FVC trends. Additionally, pharmacokinetic data from early-phase trials shown that inhaled administration achieves high local concentrations in the pulmonary parenchyma, where the antifibrotic activity is most required, while producing noticeably lower systemic drug levels than oral dosage [101].

FUTURE PERSPECTIVES:

Nanopharmaceutical systems have recently become a successful method for site-specific and regulated drug delivery [102,103,104,105]. Target-specific carriers are employed in nano-drug delivery to release medications in organs or tissues, achieving the intended release profiles and improving therapeutic results [106,107,108,109]. Intranasal delivery, also known as nose-to-lung aerosol delivery, is the administration of medications to the lungs via the nasal route. When frequent dosage is necessary, intranasal administration may be beneficial. Because the technique is noninvasive, patients may use it without outside help and it won't interfere with their normal routines. Gas distribution via intranasal administration has frequently been reported using methods such as nasal high flow treatment and low flow therapy [110]. Researchers now have more ways to comprehend the dynamics of aerosol transport, dispersion, and deposition in the alveoli throughout the lungs thanks to the computational fluid dynamics modeling technique. The formulation parameters of inhalation-based pulmonary delivery systems can be adjusted with the use of these sorts of investigations [111,112]. Potential solutions to this problem include sophisticated pharmaceutical systems that enable improved distribution of loaded bioactives to certain lung regions. These platforms comprise, among other things, solid lipid nanoparticles, polymeric micro- and nanoparticles, liposomes, and micelles that are administered by nebulizers, inhalers, intrathecal or endotracheopulmonary routes [113,114,115]. A major development in respiratory medicine, NP-based DDS offers a revolutionary method of treating both acute and chronic respiratory conditions. These cutting-edge devices have the potential to completely transform the

treatment of respiratory disorders by addressing the drawbacks of conventional treatments, thereby enhancing patient care and quality of life [116].

III. CONCLUSION:

New therapeutic strategies and pulmonary drug delivery systems have made it much easier to treat respiratory disorders. New methods, like targeted therapies and new inhalation technologies, make treatments more effective and lower the risk of systemic side effects. Continued research and the use of new technologies will make managing respiratory diseases even better and help patients around the world.

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