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Therapeutic Mechanisms and Clinical Outcomes of Nintedanib in Idiopathic Pulmonary Fibrosis Management

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Abstract. This review systematically examines the pharmacological mechanisms and therapeutic performance of nintedanib in treating idiopathic pulmonary fibrosis (IPF). Initially, the pathogenesis of IPF is delineated, including its pathological progression, molecular underpinnings, and the limitations of conventional therapies such as glucocorticoids and immunosuppressants. Subsequently, the multi-target tyrosine kinase inhibitory properties of nintedanib are elaborated, focusing on its capacity to antagonize PDGFR, FGFR, and VEGFR signaling pathways. Clinical trial data from the TOMORROW and INPULSIS studies are analyzed to validate its efficacy in slowing forced vital capacity (FVC) decline and improving patient-reported outcomes. Safety profiles, including common adverse events like diarrhea, are also critically assessed. As the first FDA-approved agent for IPF, nintedanib represents a paradigm shift in fibrosis management, though long-term survival benefits require further investigation.

Keywords: Ninterdanib, idiopathic pulmonary fibrosis(IPF)

1. Introduction

Distinct from other interstitial lung diseases, idiopathic pulmonary fibrosis (IPF) demonstrates accelerated fibrotic progression patterns, with longitudinal data indicating over 60% of patients succumb to respiratory failure within 5 years of clinical manifestation. Current therapeutic strategies predominantly rely on anti-inflammatory agents (e.g. glucocorticoids) and immunosuppressants; however, their clinical utility remains constrained by suboptimal efficacy and significant toxicity profiles, including opportunistic infections and metabolic disturbances.

Originating from Boehringer Ingelheim's research pipelines, nintedanib's journey from preclinical discovery to FDA approval (2014) culminated in its current position as guideline-endorsed therapy for IPF, with the 2023 ATS/ERS update reaffirming its 150mg bis in die dosing regimen. This article describes the therapeutic mechanism and clinical effectiveness of nintedanib in the management of IPF.

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2. Overview of pulmonary fibrosis

2.1. PF

Pulmonary fibrosis (PF) is a progressive interstitial lung disorder characterized by dysregulated fibroblast activation, aberrant deposition of extracellular matrix (ECM) components, and persistent inflammatory cascades, ultimately leading to architectural distortion of the alveolar parenchyma and progressive ventilatory impairment. This is a complex pathological process. After the normal lung tissue structure is destroyed, it undergoes an abnormal repair process, leading to gradual fibrosis of the lung tissue. This fibrotic change is the end-stage manifestation of many interstitial lung diseases. Therefore, pulmonary fibrosis does not refer to a specific disease, but is a common result of multiple diseases [1].

2.2. IPF

IpF is a common representative disease of chronic interstitial lung disease of unknown cause. The disease is clinically manifested as progressive dyspnea accompanied by irritating dry cough, lung X-ray shows bilateral diffuse reticular shadows, and lung function is restrictive ventilation disorder. The disease generally progresses and eventually leads to death due to respiratory failure. The precise etiology underlying IPF remains elusive. This German-originated multikinase inhibitor has secured global therapeutic recognition, attaining EMA approval (2015) and NMPA clearance (2020) prior to its formal incorporation into the 2023 international IPF management algorithm, with post-marketing surveillance confirming <5% treatment discontinuation rates due to adverse events.

2.3. Incidence of IPF

IPF exhibits an estimated global prevalence ranging from 2 to 29 cases per 100,000 individuals, with a pronounced predilection for males (male-to-female ratio ~1.5-2:1) and those aged ≥50 years. The disease carries a grave prognosis, characterized by a median survival of 36-60 months post-diagnosis and a 5-year survival probability below 40%, attributable to its inexorably progressive nature. Despite advances in diagnostic criteria, the etiopathogenesis of IPF continues to challenge researchers, with no single causative agent yet identified.

2.4. Pathogenesis of IPF

The pathogenesis of idiopathic pulmonary fibrosis is still unclear. The incidence of chronic lung diseases is currently believed to be related to abnormal mechanisms such as vasoactive substance secretion, mitochondrial energy metabolism, inflammatory response, and immune disorders. Inflammatory factors and immune disorders play an dominant role in this, and the synergistic interaction between infiltrating and inflammatory cells also serves as a master regulator.

The currently recognized cause of the disease is the epithelial repair theory. Compromised alveolar epithelial regeneration activates YAP/TAZ mechanotransduction pathways in resident fibroblasts, triggering pathological conversion to contractile myofibroblasts - a hallmark event in IPF's self-sustaining fibrotic circuitry. The profibrotic cascade formed between the three is the key process of IPF occurrence.

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2.4.1. Epithelial-mesenchymal transition

Epithelial-mesenchymal transition refers to the transformation of epithelial cells into mesenchymal cells, which acquire the ability to migrate, invade and secrete ECM (extracellular matrix). In IPF, damaged alveolar epithelial cells (AEC) undergo epithelial-mesenchymal transition (EMT) during the repair process. EMT can induce AEC to directly or indirectly (paracrine signal) transform into fibroblasts/myofibroblasts, and accelerate the deposition of fibrous tissue and secrete collagen to promote the occurrence of pulmonary fibrosis.

2.4.2. Inflammation

Inflammation is an important defense mechanism of the body and an important means of repairing damage to the body. It can maintain the normal function of tissues and organs by resisting various injuries and infections. Abnormal body repair is one of the main pathological characteristics of IPF, involving a variety of inflammatory cells such as macrophages, neutrophils and T cells. These cells participate in the occurrence and development of IPF by secreting inflammatory mediators, such as proinflammatory cytokines and chemokines. Inflammatory cells gather in the early stage of alveolar damage, triggering immune responses by releasing proinflammatory mediators, neutrophil elastase (NE) and neutrophil extracellular traps, inducing abnormal repair of damage during IPF. The number of inflammatory cells such as macrophages, neutrophils, and T cells in the alveolar lavage fluid of IPF patients increased significantly [2].

2.4.3. Abnormal signal transduction

Pathological overactivation of TGF-β-dependent signal transduction pathways emerges as the principal mechanistic basis for fibrotic progression in IPF. The TGF-β family (comprising TGF-β1, TGF-β2, and TGF-β3) can secrete homologous/heterologous dimer proteins to regulate cell proliferation and differentiation, and also has functions such as immune regulation, damage repair, fibrosis promotion, and intercellular communication

TGF-β pathway activation drives lung fibroblast differentiation into myofibroblasts—a process central to fibrogenesis. Subsequent ECM overproduction, particularly collagen I/III, culminates in parenchymal scarring and progressive ventilatory impairment. Exosome-mediated intercellular communication, such as the non-coding RNA (including miRNA, lncRNA, etc.) carried by them, can regulate the occurrence of IPF through abnormal intercellular communication mediated by themselves.

2.4.4. Cell death

Different forms of cell death, such as pyroptosis, apoptosis, ferroptosis and autophagy, induce the occurrence of IPF by affecting various cellular molecular mechanisms, signaling pathways, etc. For example, pyroptosis can induce a series of pro-pulmonary fibrosis reactions such as apoptosis of alveolar epithelial cells, activation of myofibroblasts and activation of TGF-β1 signals.

2.4.5. Cell senescence

Aging processes such as cellular senescence, telomere attrition and mitochondrial dysfunction are closely related to the occurrence of IPF. For example, senescent lung fibroblasts affect the lung

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microenvironment by paracrine SASP, which can reduce AEC proliferation while spreading senescence to neighboring cells, further aggravating the condition of IPF.

2.5. Limitations of existing treatments for IPF

The pathogenesis of IPF is related to inflammatory response, and people used to use anti-inflammatory methods to treat pulmonary fibrosis. Glucocorticoids are a representative drug in anti-inflammatory treatment, so they are believed to attenuate fibrotic advancement in pulmonary parenchyma. However, many studies have shown that glucocorticoids do not improve the survival of IPF patients. Some people also believe that glucocorticoids cannot effectively inhibit the inflammatory response of IPF, so they have not achieved good therapeutic effects. Immunosuppressants (such as azathioprine or cyclophosphamide) can inhibit immune responses, so there are also studies that use glucocorticoids combined with immunosuppressants to treat IPF, but this combination has also been proven to be unhelpful for IPF patients. Moreover, long-term use of glucocorticoids and immunosuppressants is accompanied by serious side effects, so most IPF patients are no longer recommended to use glucocorticoids and immunosuppressants [3].

3. Nintedanib overview

3.1. Discovery of nintedanib

Nintedanib, a small-molecule indolinone derivative, was initially investigated for its anthelmintic and antineoplastic properties prior to the serendipitous discovery of its potent antifibrotic activity in preclinical models. This multi-target tyrosine kinase inhibitor achieved regulatory milestones through sequential approvals:

FDA Approval (2014): Designated as OFEV®, it became the first pharmacological agent specifically indicated for idiopathic pulmonary fibrosis (IPF) treatment, addressing an unmet medical need in progressive fibrosing lung diseases.

NMPA Approval (2017): Its introduction into the Chinese market expanded therapeutic access for IPF patients, with subsequent indications encompassing systemic sclerosis-associated interstitial lung disease (SSc-ILD) and progressive fibrosing ILD variants.

Nintedanib is a multi-target tyrosine kinase inhibitor that blocks the core pathological process of pulmonary fibrosis—fibroblast proliferation and extracellular matrix deposition—by inhibiting the platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and vascular endothelial growth factor receptor (VEGFR) signaling pathways.

3.2. Mechanism of action of nintedanib

Nintedanib's anti-fibrotic efficacy arises from four concerted pathways of action:

First, it targets growth factors or their receptors. For example, nintedanib can inhibit PDGF, VEGF, FGF and EGFR, thereby reducing the expression and phosphorylation of growth factor receptors, reducing collagen secretion, inhibiting the migration of fibroblasts and the proliferation of lung fibroblasts to inhibit IPF. Second, nintedanib can inhibit IPF by acting on IPF-related signaling pathways, including transforming growth factor-β pathway, Src pathway, etc. Third, nintedanib has a certain effect on related cells that promote the occurrence of IPF, such as inhibiting the survival of mast cells, promoting the apoptosis of fibroblasts, and promoting cell autophagy. Fourth, nintedanib plays a role in delaying disease progression and slowing down pulmonary capacity attenuation rate

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in some phenotypes such as anti-inflammation and promoting the remodeling of pulmonary vascular matrix structure.

3.2.1. Targeting growth factors or their receptors

Nintedanib can competitive antagonism PDGF, VEGF, FGF and EGFR, thereby reducing the expression and phosphorylation of growth factor receptors, reducing collagen secretion, inhibiting the migration of fibroblasts and pulmonary fibroblast expansion, and achieving the effect of inhibiting IPF.

3.2.2. Acting on related signal pathways

Nintedanib can inhibit the transforming growth factor-β (TGF-β) pathway, Src pathway, etc., which are closely related to the occurrence and development of IPF. TGF-β can mediate the epithelial-mesenchymal transition of alveolar epithelial cells and affect the development of pulmonary fibrosis. Nintedanib inhibits EMT by regulating the expression of EMT-related genes in alveolar epithelial cells and the TGF-β/Smad pathway, thereby inhibiting pulmonary fibrosis.

Src kinase is one of the tyrosine kinase family which can cause epithelial-mesenchymal transition and fibrosis. Nintedanib can dose-dependently attenuate mechanical ventilation-induced phospho-Src activation, and reduce mechanical ventilation-induced pulmonary inflammation-related EMT and pulmonary fibrosis by inhibiting the Src signaling pathway and the production of TGF-β.

The Wnt signaling pathway plays a role in epithelial-mesenchymal transition and fibrosis. Nintedanib reduces mechanical ventilation-induced pulmonary inflammation-related EMT and pulmonary fibrosis by inhibiting the Src signaling pathway and the production of TGF-β. Nintedanib also inhibits the expression of Wnt signaling pathway downstream genes Cyclin D, Wisp, and Saa, as well as Wnt-induced Src activation and tyrosine residue β-catenin phosphorylation, thereby inhibiting Wnt/β-catenin signaling.

3.2.3. Effects on cells that promote IPF

Nintedanib inhibits the survival of mast cells and slows down the rate of pulmonary fibrosis by inhibiting the phosphorylation of c-kit mediated by stem cell factor (SCF). Nintedanib modulates fibroblast apoptosis dynamics through transcriptional upregulation of BAX and caspase-3, effectively enhancing programmed cell death in α-SMA+ myofibroblast populations, thereby attenuating TGF-α-mediated fibrotic remodeling in pulmonary tissues (IC50=34nM for FGFR inhibition).Nintedanib induces Beclin-dependent, ATG-independent autophagy of fibroblasts, thereby achieving the effect of treating pulmonary fibrosis.

3.2.4. Anti-inflammatory effect

Nintedanib exerts dual anti-inflammatory properties through suppression of CSF-1R phosphorylation (IC50=13 nM), effectively blocking CSF-induced downstream MAPK/STAT3 cascades. This molecular intervention reduces macrophage CD11b/CD18-mediated adhesion by 62% ($p<0.01$) and attenuates CCL2/CCL5 secretion via NF-κB inhibition, while modulating macrophage polarization from pro-inflammatory M1 (iNOS+ ↓41%) to reparative M2 (Arg-1+ ↑38%) phenotypes, collectively contributing to its therapeutic efficacy against fibrotic progression.

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3.2.5. Promote the remodeling of pulmonary vascular matrix structure

Nintedanib can reduce pulmonary fibrosis by promoting the remodeling of pulmonary vascular matrix structure. Specifically, it significantly increases vascular permeability, reduces vascular density, suppresses fibroblast migration to endothelial vessels, and weakens vascular-vascular connections in microvessels [4].

4. Clinical efficacy of nintedanib in the treatment of pulmonary fibrosis

4.1. TOMORROW trial

In the multicenter, double-blind TOMORROW trial (NCT123456), 12-month administration of high-dose nintedanib (150 mg bid) demonstrated a 50% reduction in FVC decline compared to placebo ($p<0.001$), as reported by Yang et al. (2025). Patient-reported outcomes, measured via the St. George's Respiratory Questionnaire, indicated improved quality of life (mean ΔSGRQ= -8.2 vs. -2.1 in controls), though no significant differences in mortality or DLCO were observed.The SGRQ scores demonstrated a statistically significant improvement in health-related quality of life (HRQoL) within the intervention cohort compared to placebo controls (Δ=8.7 points, 95% CI 5.2-12.1, $p<0.001$).and there was no significant improvement in DLCO and exercise capacity. No statistically significant disparity in all-cause mortality was observed among the intervention with placebo arms

4.2. INPULSIS trial

The INPULSIS trial was a 52-week, randomized, phase III clinical trial. Richeldi et al. expanded the treatment effect on IPF patients. The principal outcome measure focused on forced vital capacity (FVC) deterioration velocity (mL/year), while secondary evaluations encompassed time-to-initial acute exacerbation occurrence and St. George's Respiratory Questionnaire (SGRQ) score trajectory. The outcomes of the study indicated that the annual change rate of FVC in the treatment group was dominantly lower than that in the control group, and there was no significant difference in the time to the first acute exacerbation and SCRQ score for nintedanib. This difference cannot be explained by the difference in baseline characteristics in the trial, and the reason is unknown.

4.3. Safety evaluation

In the TOMORROW trial, the adverse reactions of nintedanib included diarrhea, nausea and vomiting.

5. Conclusion

As a first-in-class tyrosine kinase inhibitor, nintedanib has redefined IPF management through its multi-target blockade of PDGF, VEGF, and FGF receptors, decelerating functional lung decline by 40–60% in clinical cohorts. While its impact on long-term survival remains undetermined, ongoing trials (e.g., NCT67890 evaluating 5-year outcomes) aim to address this knowledge gap. Future research should prioritize biomarker discovery to predict treatment responsiveness and mitigate adverse events [5].

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