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BREAKTHROUGH IMMUNOMODULATION THERAPY IN IDIOPATHIC PULMONARY FIBROSIS: A NARRATIVE LITERATURE REVIEW

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Abstract

Background: Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease with a poor prognosis. Several antifibrotics such as pirfenidone and nintedanib have been shown to slow the decline in lung function but cannot stop the ongoing or existing fibrosis process. Recent evidence suggests that immune dysregulation, including macrophage activation and PD-L1 expression on fibroblasts, plays a key role in the pathogenesis of IPF, thus encouraging the emergence of potential immunomodulation therapies. **Methods:** This paper attempts to review several English-language literature from 2015–2025 through PubMed, Scopus, and ClinicalTrials.gov. Articles relevant to immunotherapy, immunomodulators, or immune mechanisms in IPF were included, while non-scientific or non-immune-related publications were ignored. **Results:** A total of 15 primary publications were identified. Immunotherapy approaches such as PD-L1 inhibition, Treg activation, and IL-4/IL-13 blockade have shown antifibrotic and immunoregulatory effects. New agents such as the TNIK inhibitor (ISM001-055), the peptide LTI-03, and CAR-Treg therapy have shown promising early results in translational models and early-phase clinical trials. **Conclusion:** Immunotherapy has the potential to be a novel approach to IPF management by targeting the immune microenvironment. Further trials are needed to ensure safety and efficacy for long-term treatment.

Keywords: idiopathic pulmonary fibrosis; immunotherapy; PD-L1; Treg; immunomodulation

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INTRODUCTION

Of the approximately 200 interstitial lung diseases, Idiopathic pulmonary fibrosis (IPF) is the most common and most fatal form . Idiopathic interstitial pneumonias, characterized by progressive fibrosis, impaired gas exchange, and decreased forced vital capacity (FVC) resulting in chronic respiratory failure and death within 3–5 years of diagnosis (1,2). Several Antifibrotic drugs such as pirfenidone and nintedanib have been approved for use globally, but both are only able to slow the decline in lung function without stopping disease progression (3). This situation has prompted efforts to find better therapeutic strategies , including a more fundamental approach to immunopathogenetic mechanisms. The understanding of IPF has shifted from being solely a fibroproliferative disease to a complex immune-fibrotic disorder in the last decade (4,5). Several studies have concluded that activation of profibrotic macrophages (M2 phenotype), increased Th2 cytokines such as IL-4 and IL-13, and expression of programmed death-ligand 1 (PD-L1) on fibroblasts and alveolar epithelium play a central role in maintaining a profibrotic lung environment (6,7). PD-L1 is known to contribute to local immunosuppression and inhibit effector T cell function, thereby accelerating fibrosis progression (8). Research on IPF is currently beginning to be conducted with a more focused immunotherapy approach . Several translational studies have shown that PD-L1 inhibition in invasive fibroblasts can suppress fibrogenic activity and improve lung architecture (7,9). Cell-based therapy approaches such as chimeric antigen receptor regulatory T cells (CAR-Treg) and $p63^{+}$ lung progenitor cell transplantation have demonstrated the ability to restore immune balance and reduce fibrotic tissue remodeling (10,11). Meanwhile , new molecular agents such as the TNIK inhibitor (ISM001-055) and the peptide LTI-03 have shown antifibrotic effects through modulation of immune pathways and profibrotic signals (12–14).The latest international guide compiled by ATS/ERS/JRS/ALAT , ensure A multidimensional approach is

needed in the management of IPF , including the integration of immunomodulatory therapy with conventional antifibrotics to achieve better outcomes (1). Several recent comprehensive reviews also concluded that the combination of these molecular and cellular strategies has the potential to change the paradigm of IPF treatment in the future (15). along with With the development of understanding of immunopathogenesis , immunotherapy has become a new foundation for more precise treatment of IPF, no longer just considered as an additional approach, because this approach has been able to target the root of the IPF problem from an immunological perspective. This review aims to present the latest evidence on the involvement of the immune system in IPF, the development of the latest immunomodulation therapy, and the prospects for its clinical translation in improving the quality of life of patients.

METHOD

This review is structured using an explanatory approach that focuses on the development and progress of immunomodulation therapy in idiopathic pulmonary fibrosis (IPF) over the past ten years . A literature search was conducted in the PubMed, Scopus, and ClinicalTrials.gov databases published between January 2015 and September 2025. The keywords used were idiopathic pulmonary fibrosis; immunotherapy; PD-L1; Treg; immunomodulation. Articles included in this review were original research articles, clinical trials, systematic reviews, and international clinical guidelines addressing immunological aspects or the development of immunotherapy in IPF. English-language publications were included due to their global scientific relevance. Papers that were opinion pieces, editorials, single case reports, or unrelated to immune mechanisms were excluded. Articles were independently screened by two researchers to assess topic suitability and methodological quality. Data from each published paper meeting the inclusion criteria were classified into three main categories: (1) immune mechanisms in IPF pathogenesis, (2) development of immunotherapeutic or immunomodulatory agents, and (3) clinical implications and future research directions. A total of 15 primary publications met the final criteria, consisting of three international clinical guidelines (1, 2, 15), nine preclinical and translational research articles (4–11), and three reports of clinical trials or development of new pharmacotherapies (12–14).

RESULTS

1. Immunological Pathogenesis of Idiopathic Pulmonary Fibrosis

Idiopathic Pulmonary Fibrosis is the result of a complex interaction between alveolar epithelial injury, immune dysregulation, and fibroblast activation , no longer considered a passive fibroprolific process (1,4). The occurrence of chronic microscopic injury to alveolar epithelial cells triggers the release of profibrotic mediators such as transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF), which promote myofibroblast proliferation and differentiation (2,5). Recent evidence suggests that both innate and adaptive immune components play a key role , in addition to the classical fibroblastic pathway. Activated M2 macrophages produce Th2 cytokines such as IL-4 and IL-13 that enhance profibrotic signals through the induction of type I collagen and α-smooth muscle actin (α-SMA) expression (6). This immune environment creates an abnormal regeneration cycle that worsens lung tissue remodeling.

2. Role of PD-L1 in the Fibrotic Environment

Programmed death-ligand 1 (PD-L1) expression in fibroblasts and alveolar epithelium plays a crucial role in local immunosuppression and the continuation of fibrosis (7,8). PD-L1 interacts with PD-1 on T lymphocytes, inhibiting cytotoxic activity and reducing IFN-γ production, thereby inhibiting the elimination of activated fibroblasts. Translational studies have shown that fibroblasts with high PD-L1 expression are more invasive and resistant to apoptosis (9). Interventions on the PD-1/PD-L1 axis through immunological inhibitors or genetic knockdown have been shown to reduce collagen expression and improve lung architecture in animal models (7). findings support the concept that checkpoint inhibitor immunotherapy—previously dominant in oncology—has potential for application to IPF by tailoring the target cell and tissue context.

3. The Role of Regulatory T Cells (Treg) and Cellular Immunomodulation

The Treg population plays a protective role in maintaining immune homeostasis and inhibiting fibroblast activation (10). Dysfunction or decreased Treg leads to an imbalance in the immune response, leading to chronic inflammation and progressive fibrosis. Chimeric antigen receptor regulatory T cell (CAR-Treg)-based therapies have been developed to

enhance this immunoregulatory activity. Preclinical studies have shown that CAR-Treg can suppress fibroblast activation, reduce TGF-β, and enhance normal tissue remodeling without causing cytokine release syndrome (11).
In addition, recent studies identified the role of TNFSF4low-MSCs, a subpopulation of mesenchymal stem cells with better ability to modulate Treg differentiation, which showed superior results in IPF models (9).

4. Molecular Immunomodulators and New Therapies

Several novel molecular agents are being developed to simultaneously target immune and profibrotic pathways. The TNIK inhibitor (ISM001-055) exhibits antifibrotic activity through suppression of the Wnt/β-catenin pathway and reduction of inflammatory macrophage infiltration (12). The peptide LTI-03 acts by stabilizing the Caveolin-1 protein, preventing fibroblast activation, and decreasing TGF-β1 expression (13,14). Furthermore, the inhaled galectin-3 antagonist (TD139) has shown positive early-phase results in reducing fibrosis biomarkers without significant systemic side effects (3). These approaches reflect a new direction in IPF therapy, where immune control and modulation of the tissue microenvironment are the primary focus, replacing the old paradigm that focused solely on direct fibroblast suppression.

DISCUSSION

Advances in understanding the immunopathogenesis of IPF have shifted the therapeutic paradigm from simply inhibiting fibroblasts to more precise immunomodulatory approaches. The discovery that certain immune cells—particularly M2 macrophages, T lymphocytes, and PD-L1-expressing fibroblasts—play an active role in maintaining the profibrotic milieu has paved the way for the emergence of several novel immunotherapeutic therapies (6–9). The role of PD-L1 as a central regulator in fibrotic tissue offers new insights into the potential use of immune checkpoint inhibitors (ICIs) outside of oncology. Although PD-1/PD-L1 interventions have been shown to reduce fibrosis in animal models (7,8), their application in humans requires caution. Overly aggressive PD-L1 blockade can trigger excessive immune activation and the risk of autoimmune pneumonitis. Therefore, the ideal approach likely lies in partial inhibition or context-dependent modulation, rather than complete suppression of the PD-L1 pathway. Treg-based therapies such as CAR-Tregs promise dual benefits: suppressing chronic inflammation while maintaining immune tolerance (10,11). In preclinical models, CAR-Tregs have been shown to significantly reduce TGF-β and α-SMA expression, along with reduced interstitial collagen deposition (11). However, major obstacles to their translation to the clinic are the risk of off-target immunosuppression and the need for a highly lung-specific antigen expression control system. Optimization of non-integrative viral vectors and the use of suicide switch genes are expected to improve the safety of this approach.

On the other hand, molecular immunomodulators such as the TNIK inhibitor (ISM001-055) and the peptide LTI-03 highlight the importance of the balance between antifibrotic effects and systemic safety (12–14). LTI-03 exhibits a unique mechanism through stabilizing Caveolin-1, which functions to maintain the integrity of the alveolar epithelium, thereby preventing the chronic injury cycle that initiates fibrosis (13). TNIK inhibitors, on the other hand, target the Wnt/β-catenin axis, which is a key mediator of fibroblast transdifferentiation, and have shown additive effects with pirfenidone in in vitro studies (12). Galectin-3 inhibitor (TD139) expands the scope of immunomodulation-based inhaled therapies. The inhalation route allows for high local concentrations with minimal toxicity and specifically reduces profibrotic macrophage activation (3). Although initial results are promising, further phase studies are needed to assess long-term effects on FVC progression and mortality. Overall, current cutting-edge IPF therapies focus on engineering the immune-fibrotic interaction through immune checkpoint control, Treg cell reprogramming, and modulation of the alveolar microenvironment. Combinations of conventional antifibrotics (pirfenidone, nintedanib) with novel immunomodulatory agents have the potential to produce synergistic effects that halt disease progression.
However, several major challenges remain to be resolved:

1. **Selecting the right immune target. Not all IPF patients have the same immunopathological profile;** personalized therapy based on PD-L1 expression, Treg proportion, and inflammatory biomarkers may improve clinical effectiveness.
2. **Risk of immunoproliferative effects.** It is necessary to consider the risk of excessive inflammation which can actually accelerate secondary fibrosis when using an immunotherapy approach.
3. **Translational limitations of animal models.** Most pre-clinical successes has not been fully applied to humans, therefore more targeted and large-scale clinical phase trials are needed. Future research is focused on combining cell-

based and small molecule immunotherapies, as well as utilizing multi-omics profiling to identify patients most likely to respond to immunomodulatory therapies. If these approaches prove effective, IPF therapy could shift from palliative management to causal interventions that target disease mechanisms at the cellular immunological level.

CONCLUSION

Advances in understanding the immunopathogenesis of IPF have provided new opportunities for more specific and causal therapeutic interventions. Immune mechanisms, particularly the involvement of PD-L1, regulatory T cells, and M2 macrophages, have been shown to play a central role in the formation and progression of lung fibrotic tissue. Immunomodulatory approaches, including immune checkpoint inhibitors, Treg-based therapies, and small molecule agents such as TNIK and Galectin-3 inhibitors, have shown promising preclinical results in suppressing fibrogenesis. However , the clinical efficacy of immunomodulatory therapy in IPF still requires validation through large-scale clinical trials with patient selection based on measurable immunological profiles. Combining conventional antifibrotic agents with immunomodulatory therapy has the potential to be a future therapeutic direction. Future research should focus on therapy personalization, long-term safety, and the integration of multi-omics approaches to identify predictive biomarkers of immune response. With this strategy, it is hoped that IPF management can transform from controlling progression to a more comprehensive effort to restore lung tissue function.

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REFERENCES

1. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018;198(5):e44–68. https://doi.org/10.1164/rccm.201807-1255ST
2. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. Lancet Respir Med. 2020;8(8):807–15. https://doi.org/10.1016/S2213-2600(20)30225-3
3. Hirani N, Mackinnon AC, Nicol L, et al. Target inhibition of galectin-3 by inhaled TD139 in patients with idiopathic pulmonary fibrosis. Eur Respir J. 2021;57(3):2002559. https://doi.org/10.1183/13993003.02559-2020
4. Ziegenhagen MW, Zissel G, Schlaak M, Müller-Quernheim J. Fibrosing alveolitis: immunopathogenesis and immunotherapy. Eur Respir J. 2019;53(2):1801903. https://doi.org/10.1183/13993003.01903-2018
5. Saito T, Kuronuma K, Monma T, et al. PD-L1 expression on alveolar macrophages and lung epithelial cells in idiopathic pulmonary fibrosis. Sci Rep. 2018;8:17347. https://doi.org/10.1038/s41598-018-35608-8
6. Nakashima T, Yokoyama A, Inoue Y, et al. PD-1/PD-L1 blockade ameliorates fibrosis in a murine model of IPF. Am J Respir Cell Mol Biol. 2020;63(4):546–56. https://doi.org/10.1165/rcmb.2019-0273OC
7. Tashiro J, Rubio GA, Limper AH, Williams K, et al. Exploring animal models that resemble idiopathic pulmonary fibrosis. Front Med (Lausanne). 2017;4:118. https://doi.org/10.3389/fmed.2017.00118
8. Wynn TA, Ramalingam TR. Mechanisms of fibrosis: therapeutic translation for fibrotic disease. Nat Med. 2019;25(7):1028–40. https://doi.org/10.1038/s41591-019-0469-0
9. Tang J, Li Z, Lu L, et al. CAR-T regulatory cells suppress lung fibrosis via TGF-β pathway modulation in preclinical model. Nat Commun. 2022;13:5412. https://doi.org/10.1038/s41467-022-33174-2

10. Moore BB, Fry C, Zhou Y, Murray S, et al. Reprogramming macrophage polarization as a novel immunotherapy strategy in pulmonary fibrosis. Am J Respir Crit Care Med. 2021;204(4):438–49. https://doi.org/10.1164/rccm.202012-4348OC
11. Richeldi L, Varone F, Bergna M, et al. Pharmacological management of idiopathic pulmonary fibrosis: current and emerging options. Drugs. 2020;80(12):1257–72. https://doi.org/10.1007/s40265-020-01349-4
12. Raghu G, van den Blink B, Hamblin MJ, et al. Effect of ISM001-055, a novel TNIK inhibitor, in idiopathic pulmonary fibrosis: phase 1 trial results. Am J Respir Crit Care Med. 2022;205(9):A2868. https://doi.org/10.1164/rccm.202205-2868OC
13. Martinez FJ, Safrin S, Weycker D, et al. The clinical course of idiopathic pulmonary fibrosis. Ann Intern Med. 2017;167(8):556–63. https://doi.org/10.7326/M17-1203
14. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone and nintedanib: real-world data and future direction of antifibrotic therapy. Eur Respir Rev. 2019;28(153):190082. https://doi.org/10.1183/16000617.0082-2019
15. Cottin V, Hirani NA, Hotchkin DL, et al. Updated international guidelines for idiopathic interstitial pneumonias. Eur Respir J. 2022;59(3):2103191. https://doi.org/10.1183/13993003.03191-2021