Preferential PDE4B Inhibition — A Step toward a New Treatment for Idiopathic Pulmonary Fibrosis

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Fibrosis, defined as the pathologic accumulation of extracellular matrix, is the final outcome of several common chronic inflammatory, immune-mediated, and metabolic diseases and accounts for up to 45% of all deaths in the industrialized world.[1] The approval of pirfenidone and nintedanib for the treatment of idiopathic pulmonary fibrosis (IPF), a rapidly progressive and fatal fibrotic condition, represented a defining moment for the development of antifibrotic therapeutic agents.[2,3] However, although these agents slow the decline in lung function, they do not halt disease progression, so IPF continues to represent a disease of high unmet clinical need.

In this issue of the *Journal*, Richeldi and colleagues[4] report on the promising results of a well-conducted phase 2, double-blind, placebo-controlled trial of BI 1015550, an oral preferential inhibitor of phosphodiesterase (PDE) 4B that has combined antifibrotic and antiinflammatory effects. The authors found that this agent, assessed as monotherapy or in combination with background antifibrotic therapy, prevented lung-function decline in patients with IPF. The antifibrotic potential and long-term side-effect profile of this agent await verification in a phase 3 trial, but the finding that it is possible to evaluate the potential of new agents on the basis of a change from baseline in the forced vital capacity (FVC) within a relatively short, 12-week treatment window, even on a background of existing antifibrotic therapy, is a major step forward. It is also worth highlighting that the results of this trial support the usefulness of adopting a Bayesian statistical approach in which historical data are used to allow more patients to be randomly assigned to receive active treatment.

The findings also raise intriguing questions regarding the mechanism by which BI 1015550 is acting, with implications for the future development of antifibrotic strategies. The currently favored paradigm for the pathogenesis of IPF proposes that this condition arises as a result of chronic epithelial microinjury and a resultant highly dysregulated wound-healing response, which is characterized by aberrant bidirectional epithelial–mesenchymal cross-talk in genetically predisposed older persons. The accumulation and persistence of hypersynthetic mesenchymal-cell populations that are derived from multiple cellular sources, including the local proliferation and differentiation of resident lung fibroblasts under the influence of potent fibroblast mitogens and differentiation factors, are key events in the emergence of fibrotic foci (the hallmark lesions of IPF) and the progression of the fibrotic remodeling process.

Inflammation is also a feature of IPF, but the contribution of inflammation to disease progression remains controversial. The negative results of multicenter trials of antiinflammatory drugs led to a view that inflammation might represent an epiphenomenon. However, newer insights, which have been facilitated in part by the application of state-of-the-art genomic approaches, have led to a reevaluation of this view, particularly with respect to the loss of T-cell and B-cell tolerance and the emergence of profibrotic macrophage populations, which are likely to collaborate with stromal cells to promote a profibrogenic microenvironment in patients with IPF.[5]

PDE4B is a member of the type IV, cyclic AMP (cAMP)–specific, cyclic nucleotide PDE family that plays a key role in signal transduction by regulating the cellular concentrations of cyclic nucleotides. The antiinflammatory and immunomodulatory effects of oral selective PDE4 inhibitors, which are mediated by the ability of these inhibitors to increase cAMP levels, underpin the approval of such agents for the treatment of certain inflammatory and autoimmune diseases, including roflumilast therapy for chronic obstructive pulmonary disease.[6] In the context of fibrosis, cAMP antagonizes profibrotic signaling cascades, and the augmentation of cAMP levels represents an important mechanism by which the endogenous antifibrotic prostanoid prostaglandin E2 inhibits virtually all pertinent functions of normal fibroblasts.[7]

PDE4 inhibition prevents the hydrolysis of

cAMP, and there is a considerable body of evidence that PDE4 inhibitors are effective at inhibiting the proliferation and differentiation of fibroblasts as well as their ability to produce extracellular matrix in the presence of an endogenous or exogenous cAMP trigger. Studies in animal models of fibrosis across organ systems support the notion that PDE4 inhibition is antifibrotic, and preclinical studies showing that the preferential targeting of PDE4B by BI 1015550 (which was developed to overcome the well-known gastrointestinal side effects that are associated with broad PDE4 inhibition) provided support for the rationale to pursue this agent in the context of IPF.[8] In terms of influencing fibroblast function, BI 1015550 blocks mitogen-induced fibroblast proliferation and also acts synergistically with nintedanib to inhibit this response. However, unlike nintedanib, BI 1015550 also inhibits transforming growth factor β1–induced myofibroblast differentiation and extracellular-matrix expression,[8] a core fibrogenic pathway in multiple fibrotic conditions.[1]

In terms of the encouraging results of the current phase 2 trial, it is not possible to determine whether this agent exerts its potential beneficial effects by means of antiinflammatory, immunomodulatory, or multiple antifibrotic approaches or indeed by a combination of all these. However, together with the proven effectiveness of existing antifibrotic agents, which are likely to act on several targets or disease pathways, the continued exploration of agents that affect multiple collaborating mechanisms in IPF and potentially other fibrotic conditions continues to hold considerable promise.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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1. Henderson NC, Rieder F, Wynn TA. Fibrosis: from mechanisms to medicines. Nature 2020;587:555-66.
2. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2083-92.
3. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071-82.
4. Richeldi L, Azuma A, Cottin V, et al. Trial of a preferential phosphodiesterase 4B inhibitor for idiopathic pulmonary fibrosis. N Engl J Med 2022;386:2178-87.
5. Heukels P, Moor CC, von der Thüsen JH, Wijsenbeek MS, Kool M. Inflammation and immunity in IPF pathogenesis and treatment. Respir Med 2019;147:79-91.
6. Giembycz MA, Field SK. Roflumilast: first phosphodiesterase 4 inhibitor approved for treatment of COPD. Drug Des Devel Ther 2010;4:147-58.
7. Huang S, Wettlaufer SH, Hogaboam C, Aronoff DM, Peters-Golden M. Prostaglandin E(2) inhibits collagen expression and proliferation in patient-derived normal lung fibroblasts via E prostanoid 2 receptor and cAMP signaling. Am J Physiol Lung Cell Mol Physiol 2007;292(2):L405-L413.
8. Herrmann FE, Hesslinger C, Wollin L, Nickolaus P. BI 1015550 is a PDE4B inhibitor and a clinical drug candidate for the oral treatment of idiopathic pulmonary fibrosis. Front Pharmacol 2022;13:838449.

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Monoclonal Antibodies with Extended Half-Life to Prevent Covid-19

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Early treatment (i.e., soon after the onset of Covid-19 symptoms) with monoclonal antibodies that target the SARS-CoV-2 spike protein reduces the risks of Covid-19–related hospitalization and death.[1-3] Yet, despite the success of these interventions, in response to continued pressure from human immune responses, the SARS-CoV-2 spike protein has evolved to evade almost all available monoclonal antibody–based drugs.[4]

In this issue of the *Journal*, Levin et al.[5] report on the use of AZD7442 (tixagevimab–cilgavimab) for the prevention of Covid-19. Tixagevimab and cilgavimab are monoclonal antibodies that target the SARS-CoV-2 spike protein. Both were derived from B cells obtained from persons infected with SARS-CoV-2.[6] The non–antigen-binding fragment (Fc fragment) of these antibodies was modified so that they would have an extended half-life and decreased immune effector