Review

Potential of phosphodiesterase 4B inhibitors in the treatment of interstitial lung disease associated with autoimmune diseases

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ABSTRACT

Patients with autoimmune disease-related interstitial lung disease may develop pulmonary fibrosis, which may become progressive. Progressive pulmonary fibrosis (PPF) is associated with poor outcomes. Antifibrotic therapies have shown efficacy as treatments for PPF in patients with autoimmune diseases, but new treatments are needed to slow or halt disease progression. Phosphodiesterases (PDEs) are enzymes that mediate the hydrolysis of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Pre-clinical data suggest that preferential inhibition of PDE4B has the potential to slow the progression of pulmonary fibrosis by inhibiting inflammatory and fibrotic pathways, with a lower risk of gastrointestinal adverse events than associated with pan-PDE4 inhibitors. Nerandomilast (BI 1015550) is a preferential PDE4 inhibitor that has demonstrated anti-inflammatory and antifibrotic effects in pre-clinical studies. In a phase II trial in patients with idiopathic pulmonary fibrosis, nerandomilast (given alone or on top of background antifibrotic therapy) prevented a decrease in lung function over 12 weeks with an acceptable safety and tolerability profile. The phase III FIBRONEER-ILD trial is evaluating the efficacy and safety of nerandomilast, given alone or on top of nintedanib, in patients with PPF, including PPF associated with autoimmune diseases. In this article, we review the potential of PDE4B inhibition in the treatment of ILD associated with autoimmune diseases, including the pre-clinical and early clinical data available to date.

Introduction

Patients with systemic autoimmune diseases are at risk of developing interstitial lung disease (ILD) (1, 2). The pathogenesis of ILD associated with autoimmune diseases involves inflammatory and fibrotic pathways (3). Inflammatory features, such as ground glass opacities, and fibrotic features such as traction bronchiectasis, may be evident on a high-resolution computed tomography (HRCT) scan (4, 5). In patients with ILD due to rheumatoid arthritis (RA-ILD), the pattern most frequently observed on HRCT is usual interstitial pneumonia (UIP) (6). In other autoimmune disease-related ILDs, including ILD associated with systemic sclerosis (SSc-ILD) and myositis, the pattern most frequently observed is non-specific interstitial pneumonia (NSIP) (7-9).

Patients with fibrotic ILD may develop progressive pulmonary fibrosis (PPF). A definition of PPF was proposed in a clinical practice guideline published by international pulmonology societies in 2022 (10). In this guideline, PPF was defined as the unexplained occurrence of at least two of the following: 1) physiologic progression of disease measured using pulmonary function tests; 2) radiological indicators of disease progression; 3) deteriorating respiratory symptoms. Various studies assessing PPF using similar criteria have demonstrated that PPF portends a poor prognosis, with patients facing deteriorating lung function, worsening respiratory symptoms, and earlier mortality (11-15).

Several studies have demonstrated that patients with autoimmune disease-related ILDs who develop PPF have poor outcomes (16-19). For example, in an analysis of claims data involving 2521 patients with progressive fibrosing RA-ILD and 907 patients with progressive fibrosing SSc-ILD, the median survival rates after eight years of follow-up were 28.9% and 26.7%, respectively

(17). Patients with autoimmune disease-related PPF based on decline in lung function have an increased risk of mortality (18, 19). Acute exacerbations of ILD, defined as acute worsening or development of dyspnea, new bilateral ground-glass opacity and/or consolidation on CT, with the deterioration not fully explained by cardiac failure or fluid overload, may occur in patients with autoimmune disease-related ILD and are associated with high mortality (20, 21).

Many patients with autoimmune disease-associated ILD receive immunomodulatory therapy, but the efficacy of these therapies in slowing the progression of pulmonary fibrosis remains uncertain. Notably, pulmonary fibrosis linked to autoimmune disease demonstrates a higher incidence within Black populations and has been associated with an increased utilisation of immunomodulatory interventions among individuals of this racial demographic (22). The use of cyclophosphamide, mycophenolate and tocilizumab in the treatment of SSc-ILD is supported by evidence from randomised controlled trials (23-26). For other autoimmune disease-associated ILDs, most of the evidence to suggest a benefit of immunomodulatory therapies comes from retrospective or uncontrolled studies (27-29), but evidence from randomised controlled trials is building. In the randomised RECITAL trial in patients with severe or progressive autoimmune disease-associated ILDs, forced vital capacity (FVC) improved over 24 weeks in patients who received rituximab (mean increase of 97 mL) or cyclophosphamide (mean increase of 99 mL) (30). Fewer adverse events were reported in the rituximab group than in the cyclophosphamide group (30). In the randomised EVER-ILD trial in patients with autoimmune disease-associated ILDs or idiopathic interstitial pneumonia and an NSIP pattern, patients treated with mycophenolate and rituximab showed an increase in FVC % predicted of 1.6 over 6 months compared to a decline in FVC % predicted of 2.0 among patients on mycophenolate and placebo (31). Viral infections were reported more frequently in patients treated with mycophenolate and rituximab than mycophenolate and placebo (31). In both the RECITAL and EVER-ILD trials, the effect of treatment appeared to be consistent across subgroups by diagnosis (30, 31).

Antifibrotic therapies (nintedanib and pirfenidone), originally developed as treatments for idiopathic pulmonary fibrosis (IPF) (32, 33), have shown efficacy as treatments for PPF in patients with autoimmune diseases (34-36). Based on the results of the INBUILD trial (37), nintedanib was approved by the FDA, EMA and other regulators for the treatment of progressive fibrosing ILDs of any aetiology. A clinical practice guideline published by international pulmonology societies in 2022 gave a conditional recommendation for the use of nintedanib in patients with PPF who have failed standard management for fibrotic ILD (10).

Even for patients receiving standard of care therapy, PPF continues to progress and is associated with poor outcomes (38-40). There is a need for new treatments that can be used alone or with existing therapies to slow or even halt the progression of PPF. In this article, we review the potential of phosphodiesterase 4B inhibition as a treatment for PPF associated with autoimmune diseases.

Phosphodiesterase 4 inhibitors

Phosphodiesterases (PDEs) are enzymes that mediate the hydrolysis of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) (41). cAMP and cGMP are second messengers that are central to signal transduction cascades regulating several processes, including cellular proliferation and differentiation, and inflammation (41). The PDE superfamily comprises 11 gene subfamilies (PDE1 to PDE11), which vary in their distribution in cell and tissue types (41). PDE4 is highly expressed in the brain (42), cardiovascular tissues (43), smooth muscle (44, 45), keratinocytes (46), and immune cells, including inflammatory cells involved in the pathogenesis of inflammatory lung diseases (47-50). PDE4 is also expressed in lung adenocarcinoma, squamous and large cell carcinoma cell lines (51).

Inhibition of PDE4 increases levels of cAMP, reducing the release of pro-inflammatory mediators and increasing the synthesis of anti-inflammatory cytokines (52). PDE4 inhibition has shown anti-inflammatory effects in preclinical studies (53). In murine macrophages, inhibition of PDE4 decreased production of inflammatory mediators such as nitric oxide, tumou Ir necrosis factor (TNF)-α, and interleukin-1β (54). In mice with bleomycin-induced pulmonary fibrosis, PDE4 inhibition reduced the total number of alveolar inflammatory cells and the number of macrophages and lymphocytes in bronchoalveolar lavage fluid (BALF) (55). Pre-clinical studies have also shown that PDE4 inhibitors have antifibrotic effects and may reduce fibrotic remodelling in the lung (55-58). In mice with bleomycin-induced pulmonary fibrosis, PDE4 inhibition reduced the extent of fibrosis in the lungs (55). In mice with fibrosis induced by type II alveolar epithelial cell injury via intraperitoneal Diphtheria toxin, PDE4 inhibition ameliorated lung collagen accumulation and weight loss, with effects that were equivalent to those of pirfenidone or nintedanib (58). These activities suggest a potential role for PDE4 inhibition in the treatment of PPF.

The PDE4B subtype

The PDE4B subtype has five variants (PDE4B1 to 5) and is widely distributed, including in the brain (42, 59), lung (59, 60), heart (43, 61) and immune cells (47, 50, 62) (Table I). PDE4B plays roles in inflammation and fibrosis. Studies in mouse peritoneal macrophages and monocytes/macrophages from BALF have shown that lipopolysaccharide (LPS) stimulation of Toll-like receptors leads to upregulation of PDE4B but not PDE4A or PDE4D (63, 64). Ablation of the gene for PDE4B blunted the TNF-α response (63,64). PDE4B is essential for the development of airway hyperresponsiveness and induction of T helper 2 (Th2)-cell functions in bronchial lymph node cells from mice (65). In human lung fibroblasts, knockdown of PDE4A or PDE4B inhibited proliferation and differentiation into myofibroblasts, while knockdown

Table I. Effects of PDE4B inhibition.

Cell/tissue	Effects of PDE4B inhibition
Lungs	• Reduced profibrotic activity of lung fibroblasts from patients with IPF; attenuated TGF-β-induced expression of genes for collagen and fibronectin; reduced bFGF plus IL-1β-induced cell proliferation (71) • Reduced silica-induced macrophage influx into the BALF (Suncus murinus) (71) • Reduced LPS-induced neutrophil influx into the BALF (Suncus murinus and Wistar rats) (71) • Improved lung volume, reduced tissue density, reversed transcription changes relevant to fibrosis (rats) (72). • Reduced IPF-associated protein levels in human myofibroblasts and small airway epithelial cells (72).
Brain	• Reduced Th2 differentiation and increased Th17 differentiation in dendritic cells (mouse) (81) • Reduced striatal dopamine and 5-hydroxytryptamine activity, associated with reduced pre-pulse inhibition and motor activity (PDE4B knockout mouse) (82) • Reduced anxiogenic-like behaviour (PDE4B knockout mouse) (83)
Cardiovascular	• Reduced neutrophil-mediated inflammation, improved microvascular perfusion, and reduced infarct size after myocardial ischaemia-reperfusion (PDE4B knockout mouse). Reversed acute myocardial infarction-induced endothelium dysfunction in coronary small arteries (PDE4B knockout mouse and human) (61) • Improved cardiac contractility (PDE4B knockout mouse) (61, 84)
Gastrointestinal	• The emetic potential of PDE4B inhibitors is lower than that of pan-PDE4 inhibitors (Suncus murinus) (71)
Peripheral blood mononuclear cells	• Reduced LPS-induced release of TNF-αand phytohemagglutinin P-induced release of IL-2 (human) (71)
Whole blood	• Reduced LPS-induced release of TNF-α (rat and human) and increased LPS-induced release of IL-6 (rat) (71)

BALF: bronchoalveolar lavage fluid; Col: collagen type; FGF: fibroblast growth factor; FN: fibronectin; IL-1β: interleukin-1ß; IL-2: interleukin-2; IPF: idiopathic pulmonary fibrosis; LPS: lipopolysaccharide; PDE4B: phosphodiesterase 4B; TGF-β: transforming growth factor-ß; Th: T helper; TNF-α: tumour necrosis factor-α.

of PDE4D was ineffective (66). These data suggest that preferential inhibition of PDE4B has the potential to slow the progression of pulmonary fibrosis by inhibiting inflammatory and fibrotic pathways (Fig. 1).

Pan-PDE4 inhibitors are associated with gastrointestinal adverse events (67, 68). Pre-clinical studies suggest that inhibition of PDE4D, but not PDE4B, may promote emesis (69, 70), suggesting that preferential PDE4B inhibitors will have fewer gastrointestinal adverse events than pan-PDE4 inhibitors. In *Suncus murinus*, after administration of the PDE4B inhibitor nerandomilast (at 10 times the effective dose for half-maximal inhibition [ED_{50}]) to 24 animals, 21% showed emesis, compared to 42% of animals treated with the pan-PDE4 inhibitor roflumilast at 10 times the effective dose for ED_{50} (71).

Nerandomilast, a preferential PDE4B inhibitor

Nerandomilast is a preferential PDE4 inhibitor that has approximately ten-fold selectivity for PDE4B *versus* PDE4D (71). Nerandomilast has demonstrated anti-inflammatory effects in pre-clinical studies (71). In human peripheral blood mononuclear cells, nerandomilast inhibited synthesis of LPS-induced TNF-α and phytohemagglutinin-induced interleukin-2 (71). In human and rat whole blood, nerandomilast inhibited LPS-induced synthesis of TNF-α. In mice, nerandomilast inhibited LPS-induced TNF-α release. In *Suncus murinus* and rats, nerandomilast inhibited LPS-induced neutrophil influx into the BALF (71). Pre-clinical studies have also shown that nerandomilast has antifibrotic effects (71). In lung fibroblasts from patients with IPF, nerandomilast inhibited transforming growth factor (TGF)-β1-stimulated transformation into myofibroblasts, expression of mRNAs for extracellular matrix proteins, and cell proliferation induced by interleukin-1β plus fibroblast growth factor. A combination of nerandomilast and nintedanib showed a synergistic effect on cell proliferation in this model. In mice with bleomycin-induced pulmonary fibrosis, nerandomilast was associated with an improvement in FVC and a reduction in fibrotic tissue in the lungs (71). In rats with bleomycin-induced pulmonary fibrosis, nerandomilast was associated with an improvement in lung volume and reduction in tissue density, and reversed transcription changes relevant to fibrosis (72). In a Phase II trial in patients with IPF, nerandomilast had small but significant effects on the expression of genes associated with inflammation and fibrosis, which correlated with changes in FVC over 12 weeks (73).

Phase I and II trials of nerandomilast

In Phase I studies in healthy subjects and patients with IPF, single rising doses of nerandomilast 36 mg and 48 mg and multiple rising doses of nerandomilast 6 mg and 12 mg twice daily (BID) over 14 days had an acceptable safety and tolerability profile (74). A Phase II randomised placebo-controlled trial of nerandomilast 18 mg BID was conducted in 147 patients with IPF (75). Among 73 patients not on background antifibrotic therapy, mean age was 70.6 years, FVC was 81.0% predicted and diffusing capacity of the lungs for carbon monoxide (DLco) was 50.7% predicted, while among 74 patients on background antifibrotic therapy, mean age was 68.7 years, FVC was 74.4% predicted and DLco

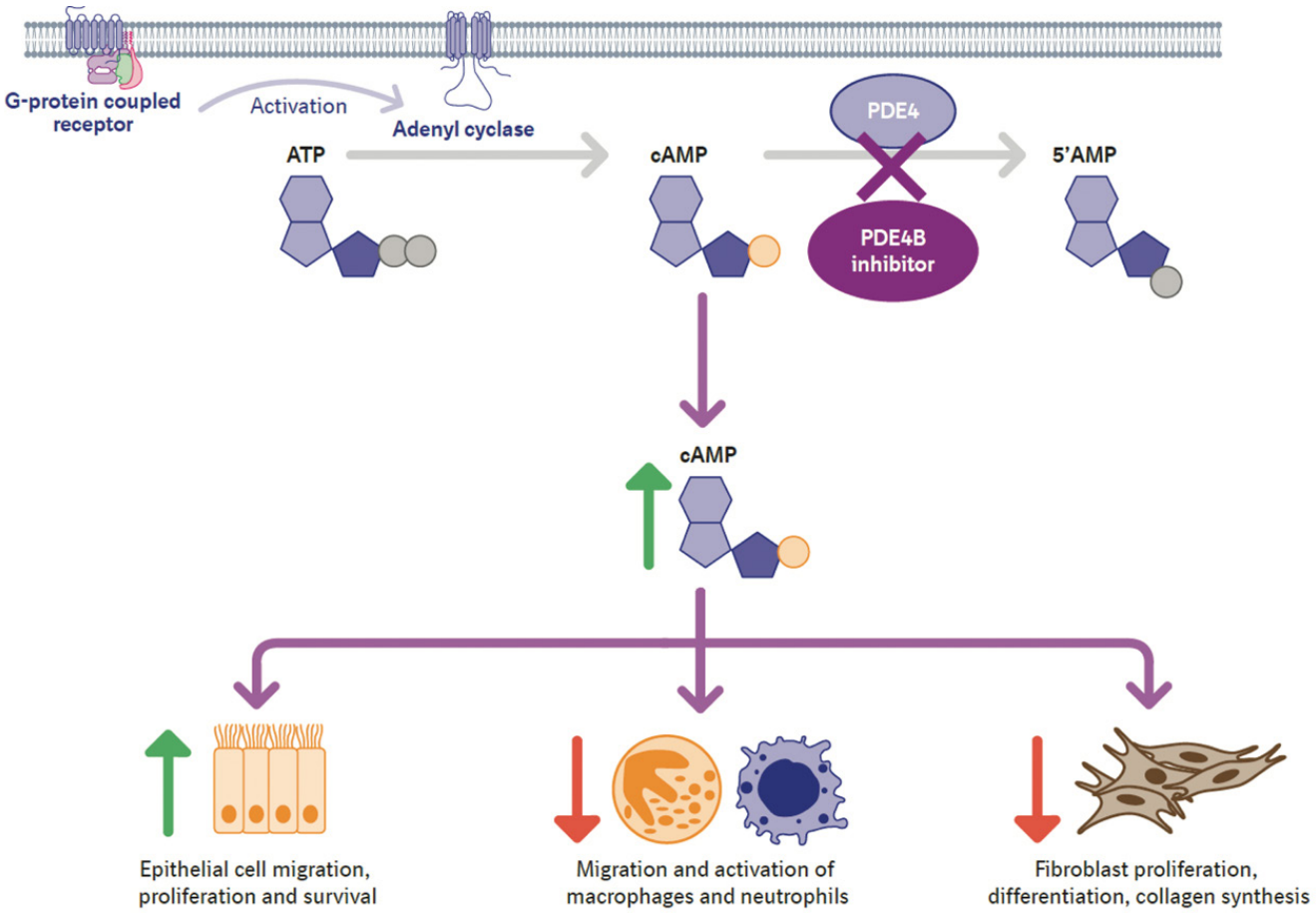

Fig. 1. Mechanism of action of phosphodiesterase 4B (PDE4B) inhibition in the treatment of pulmonary fibrosis.

was 48.4% predicted (75). Taken alone or on top of background antifibrotic therapy (nintedanib or pirfenidone), nerandomilast prevented a decrease in lung function over 12 weeks. Among patients not taking background antifibrotic therapy, the median change in FVC from baseline to week 12 was 5.7 mL in the nerandomilast group and -81.7 mL in the placebo group. Among patients taking background antifibrotic therapy, the median change in FVC was 2.7 mL in the nerandomilast group and –59.2 mL in the placebo group (75). The pattern of change in forced expiratory volume in one second (FEV_1) was similar to the pattern of change in FVC over 12 weeks, suggesting that the early treatment effect of BI 1015550 in patients with IPF was not mediated by bronchodilation (76). A *post-hoc* analysis suggested that there was an additive effect of nerandomilast and nintedanib: the adjusted mean increase in FVC at week 12 in patients treated with nerandomilast was 6.1 mL in patients not taking background antifibrotic therapy and 23.4 mL in patients taking nintedanib (77).

The most common adverse events reported in the Phase II trial were gastrointestinal disorders, which were reported, respectively, in 27% and 16% of those who received nerandomilast and placebo in the absence of background antifibrotic therapy, and in 37% and 32% of those who received nerandomilast and placebo plus background antifibrotic therapy (75). The most frequent adverse event was diarrhea. Adverse events led to discontinuation of nerandomilast in 6% of patients who received nerandomilast and no background antifibrotic therapy and in 20% of those who received nerandomilast plus background antifibrotic therapy (75).

The FIBRONEER trials

The Phase III trials of nerandomilast are known as the FIBRONEER trials. FIBRONEER-ILD (NCT05321082) is a randomised placebo-controlled trial investigating the efficacy and safety of nerandomilast, with or without background nintedanib, in patients with PPF of any aetiology (but not IPF) (78). Participants must meet one of the following criteria for ILD progression within the prior 24 months: relative decline in FVC% predicted of ≥10%; decline in FVC% predicted of ≥5 to <10% with worsened respiratory symptoms and/or increased extent of fibrotic changes on imaging; worsened respiratory symptoms and an increased extent of fibrotic changes on imaging. These are the same inclusion criteria used in the INBUILD trial and differ from the criteria for the definition of PPF published by international pulmonology societies in 2022 (10). Participants must have received nintedanib for ≥12 weeks (stable therapy), or not received nintedanib for ≥8 weeks (naive or previously discontinued), prior to screening. Treatment with pirfenidone is not permitted, as this is not a licensed treatment for PPF other than IPF. The use of certain immunomodulatory agents

(cyclophosphamide, tocilizumab, mycophenolate, rituximab) and high-dose steroids (prednisone >15 mg/day or equivalent) are not permitted at randomisation; patients on stable treatment with other immunomodulatory agents may continue to take them. During the treatment period, prednisone >15 mg/day or equivalent can be prescribed in case of suspected acute exacerbation and, after 6 months, changes in immunomodulatory treatment are permitted to manage worsening of underlying disease. Among patients not receiving nintedanib at enrolment, initiation of nintedanib is allowed after 12 weeks in case of disease worsening or acute exacerbation of ILD.

Participants will be randomised 1:1:1 to receive nerandomilast 9 mg BID, BI 1015550 18 mg BID, or placebo BID until the last patient has reached week 52. It is planned that 1041 patients will be enrolled. The primary endpoint is the absolute change from baseline in FVC (mL) at week 52. The key secondary endpoint is the time to first acute exacerbation, hospitalisation for respiratory cause, or death over the whole trial. Changes in cough, dyspnea and fatigue scores using the Living with Pulmonary Fibrosis (L-PF) questionnaire (79) at week 52 will be measured as other secondary endpoints.

A Phase III trial in patients with IPF, FIBRONEER-IPF (NCT05321069), is also being conducted, with a similar design, but with background therapy with nintedanib or pirfenidone being permitted (80).

Conclusions

PPF in patients with autoimmune diseases is associated with substantial morbidity and mortality. There is a need for additional treatments for PPF associated with autoimmune diseases that can be used alone or in combination with existing therapies. Inhibition of PDE4B has anti-inflammatory and antifibrotic effects, suggesting that PDE4B inhibitors have the potential to be effective in the treatment of PPF associated with autoimmune diseases. The FIBRONEER-ILD trial will evaluate the efficacy and safety of the preferential PDE4B inhibitor nerandomilast in patients with PPF, including PPF associated with autoimmune diseases.

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References

1. SAMBATARO G, SAMBATARO D, SPICUZZA L *et al*.: Progression and prognosis of interstitial pneumonia with autoimmune features: a longitudinal, prospective, multi-centre study. *Clin Exp Rheumatol* 2023; 41(5): 1140-48. https://doi.org/10.55563/clinexprheumatol/lycdca
2. SHAH GUPTA R, KOTECI A, MORGAN A, GEORGE PM, QUINT JK: Incidence and prevalence of interstitial lung diseases worldwide: a systematic literature review. *BMJ Open Respir Res* 2023; 10(1): e001291. https://doi.org/10.1136/bmjresp-2022-001291
3. WELLS AU, DENTON CP: Interstitial lung disease in connective tissue disease--mechanisms and management. *Nat Rev Rheumatol* 2014; 10(12): 728-39. https://doi.org/10.1038/nrrheum.2014.149
4. PALMUCCI S, GALIOTO F, FAZIO G *et al*.: Clinical and radiological features of lung disorders related to connective-tissue diseases: a pictorial essay. *Insights Imaging* 2022;13(1):108. https://doi.org/10.1186/s13244-022-01243-2
5. WALSH SLF, LAFYATIS RA, COTTIN V: Imaging features of autoimmune disease-related interstitial lung diseases. *J Thoracic Imaging* 2023; 38 (Suppl 1): S30-37. https://doi.org/10.1097/rti.0000000000000734
6. SALAFFI F, CAROTTI M, DI CARLO M, TARDELLA M, GIOVAGNONI A: High-resolution computed tomography of the lung in patients with rheumatoid arthritis: prevalence of interstitial lung disease involvement and determinants of abnormalities. *Medicine* (Baltimore) 2019; 98(38): e17088. https://doi.org/10.1097/md.0000000000017088
7. DESAI SR, VEERARAGHAVAN S, HANSELL DM *et al*.: CT features of lung disease in patients with systemic sclerosis: comparison with idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia. *Radiology* 2004; 232(2): 560-67. https://doi.org/10.1148/radiol.2322031223
8. MARIE I, HATRON PY, DOMINIQUE S, CHERIN P, MOUTHON L, MENARD JF: Short-term and long-term outcomes of interstitial lung disease in polymyositis and dermatomyositis: a series of 107 patients. *Arthritis Rheum* 2011; 63(11): 3439-47. https://doi.org/10.1002/art.30513
9. ATIENZA-MATEO B, REMUZGO-MARTÍNEZ S, MORA CUESTA VM *et al*.: The spectrum of interstitial lung disease associated with autoimmune diseases: data of a 3.6-year prospective study from a referral center of interstitial lung disease and lung transplantation. *J Clin Med* 2020; 9(6): 1606. https://doi.org/10.3390/jcm9061606
10. RAGHU G, REMY-JARDIN M, RICHELDI L *et al*.: Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2022; 205(9): e18-47. https://doi.org/10.1164/rccm.202202-0399st
11. BROWN KK, INOUE Y, FLAHERTY KR *et al*.: Predictors of mortality in subjects with progressive fibrosing interstitial lung diseases. *Respirology* 2022; 27(4): 294-300. https://doi.org/10.1111/resp.14231
12. HAMBLY N, FAROOQI MM, DVORKIN-GHEVA A *et al*.: Prevalence and characteristics of progressive fibrosing interstitial lung disease in a prospective registry. *Eur Respir J* 2022; 60(4): 2102571. https://doi.org/10.1183/13993003.02571-2021
13. TAKEI R, BROWN KK, YAMANO Y *et al*.: Prevalence and prognosis of chronic fibrosing interstitial lung diseases with a progressive phenotype. Respirology 2022; 27(5): 333-40. https://doi.org/10.1111/resp.14245
14. KHOR YH, FAROOQI M, HAMBLY N, KOLB M, RYERSON CJ: Patient characteristics and survival for progressive pulmonary fibrosis using different definitions. *Am J Respir Crit Care Med* 2023; 207(1): 102-5. https://doi.org/10.1164/rccm.202205-0910le
15. PUGASHETTI JV, ADEGUNSOYE A, WU Z *et al*.: Validation of proposed criteria for progressive pulmonary fibrosis. *Am J Respir Crit Care Med* 2023; 207(1): 69-76. https://doi.org/10.1164/rccm.202201-0124oc
16. REISETER S, GUNNARSSON R, MOGENS AALØKKEN T *et al*.: Progression and mortality of interstitial lung disease in mixed connective tissue disease: a long-term observational nationwide cohort study. *Rheumatology* (Oxford) 2018; 57(2): 255-62. https://doi.org/10.1093/rheumatology/kex077
17. NASSER M, LARRIEU S, BOUSSEL L *et al*.: Estimates of epidemiology, mortality and disease burden associated with progressive fibrosing interstitial lung disease in France (the PROGRESS study). *Respir Res* 2021; 22(1): 162. https://doi.org/10.1186/s12931-021-01749-1
18. SOLOMON JJ, CHUNG JH, COSGROVE GP *et al*.: Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J* 2016; 47(2): 588-96. https://doi.org/10.1183/13993003.00357-2015
19. GOH NS, HOYLES RK, DENTON CP *et al*.: Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. *Arthritis Rheumatol* 2017; 69(8): 1670-78. https://doi.org/10.1002/art.40130
20. ENOMOTO N, NAOI H, MOCHIZUKA Y *et al*.: Frequency, proportion of PF-ILD, and prognostic factors in patients with acute exacerbation of ILD related to systemic autoimmune diseases. *BMC Pulm Med* 2022; 22(1): 387. https://doi.org/10.1186/s12890-022-02197-3
21. HOZUMI H, KONO M, HASEGAWA H *et al*.:

Acute exacerbation of rheumatoid arthritis-associated interstitial lung disease: mortality and its prediction model. *Respir Res* 2022; 23(1): 57. https://doi.org/10.1186/s12931-022-01978-y
22. ADEGUNSOYE A, FREIHEIT E, WHITE EN *et al*.: Evaluation of pulmonary fibrosis outcomes by race and ethnicity in US adults. *JAMA Netw Open* 2023; 6(3): e232427. https://doi.org/10.1001/jamanetworkopen.2023.2427
23. HOYLES RK, ELLIS RW, WELLSBURY J *et al*.: A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum* 2006; 54(12): 3962-70. https://doi.org/10.1002/art.22204
24. TASHKIN DP, ELASHOFF R, CLEMENTS PJ *et al*.: Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006; 354(2): 2655-66. https://doi.org/10.1056/nejmoa055120
25. TASHKIN DP, ROTH MD, CLEMENTS PJ *et al*.: Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. *Lancet Respir Med* 2016; 4(9): 708-19. https://doi.org/10.1016/s2213-2600(16)30152-7
26. ROOFEH D, LIN CJF, GOLDIN J *et al*.: Tocilizumab prevents progression of early systemic sclerosis-associated interstitial lung disease. *Arthritis Rheumatol* 2021; 73(7): 1301-10. https://doi.org/10.1002/art.41668
27. DOYLE TJ, DHILLON N, MADAN R *et al*.: Rituximab in the treatment of interstitial lung disease associated with antisynthetase syndrome: a multicenter retrospective case review. *J Rheumatol* 2018; 45(6): 841-50. https://doi.org/10.3899/jrheum.170541
28. HUAPAYA JA, SILHAN L, PINAL-FERNANDEZ I *et al*.: Long-term treatment with azathioprine and mycophenolate mofetil for myositis-related interstitial lung disease. *Chest* 2019; 156(5): 896-906. https://doi.org/10.1016/j.chest.2019.05.023
29. MATSON SM, BAQIR M, MOUA T *et al*.: Treatment outcomes for rheumatoid arthritis-associated interstitial lung disease: a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest* 2023; 163(4): 861-69. https://doi.org/10.1016/j.chest.2022.11.035
30. MAHER TM, TUDOR VA, SAUNDERS P *et al*.: Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial. *Lancet Respir Med* 2023; 11(1): 45-54. https://doi.org/10.1016/s2213-2600(22)00359-9
31. MANKIKIAN J, CAILLE A, REYNAUD-GAUBERT M *et al*.: Rituximab and mycophenolate mofetil combination in patients with interstitial lung disease (EVER-ILD): a double-blind, randomised, placebo-controlled trial. *Eur Respir J* 2023; 61(6): 2202071. https://doi.org/10.1183/13993003.02071-2022
32. 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(22): 2083-92. https://doi.org/10.1056/nejmoa1402582
33. RICHELDI L, DU BOIS RM, RAGHU G *et al*.: Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370(22): 2071-82. https://doi.org/10.1056/nejmoa1402584
34. DISTLER O, HIGHLAND KB, GAHLEMANN M *et al*.: Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med* 2019; 380(26): 2518-28. https://doi.org/10.1056/nejmoa1903076
35. MATTESON EL, KELLY C, DISTLER JHW *et al*.: Nintedanib in patients with autoimmune disease-related progressive fibrosing interstitial lung diseases: subgroup analysis of the INBUILD trial. *Arthritis Rheumatol* 2022; 74(6): 1039-47. https://doi.org/10.1002/art.42075
36. SOLOMON JJ, DANOFF SK, WOODHEAD FA *et al*.: Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet Respir Med* 2023; 11(1): 87-96. https://doi.org/10.1016/s2213-2600(22)00260-0
37. FLAHERTY KR, WELLS AU, COTTIN V *et al*.: Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019; 381(18): 1718-27. https://doi.org/10.1056/nejmoa1908681
38. ALLANORE Y, VONK MC, DISTLER O *et al*.: Continued treatment with nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from SENSCIS-ON. *Ann Rheum Dis* 2022; 81(12): 1722-9. https://doi.org/10.1136/ard-2022-222564
39. FLAHERTY KR, WELLS AU, COTTIN V *et al*.: Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. *Eur Respir J* 2022; 59(3): 2004538. https://doi.org/10.1183/13993003.04538-2020
40. WUYTS WA, BONELLA F, CHAUDHURI N *et al*.: Continued nintedanib treatment in patients with progressive pulmonary fibrosis: data from INBUILD-ON. Poster at European Respiratory Society International Congress, 2023: https://www.globalmedcomms.com/respiratory/ers2023/wuyts1.
41. AZEVEDO MF, FAUCZ FR, BIMPAKI E *et al*.: Clinical and molecular genetics of the phosphodiesterases (PDEs). *Endocr Rev* 2014; 35(2): 195-233. https://doi.org/10.1210/er.2013-1053
42. PÉREZ-TORRES S, MIRÓ X, PALACIOS JM, CORTÉS R, PUIGDOMÉNECH P, MENGOD G: Phosphodiesterase type 4 isozymes expression in human brain examined by in situ hybridization histochemistry and[3H]rolipram binding autoradiography. Comparison with monkey and rat brain. *J Chem Neuroanat* 2000; 20(3-4): 349-74. https://doi.org/10.1016/s0891-0618(00)00097-1
43. RICHTER W, XIE M, SCHEITRUM C, KRALL J, MOVSESIAN MA, CONTI M: Conserved expression and functions of PDE4 in rodent and human heart. *Basic Res Cardiol* 2011; 106(2): 249-62. https://doi.org/10.1007/s00395-010-0138-8
44. MÉHATS C, JIN SL, WAHLSTROM J, LAW E, UMETSU DT, CONTI M: PDE4D plays a critical role in the control of airway smooth muscle contraction. *FASEB J* 2003; 17(13): 1831-41. https://doi.org/10.1096/fj.03-0274com
45. GROWCOTT EJ, SPINK KG, REN X, AFZAL S, BANNER KH, WHARTON J: Phosphodiesterase type 4 expression and anti-proliferative effects in human pulmonary artery smooth muscle cells. *Respir Res* 2006; 7(1): 9. https://doi.org/10.1186/1465-9921-7-9
46. CHUJOR CS, HAMMERSCHMID F, LAM C: Cyclic nucleotide phosphodiesterase 4 subtypes are differentially expressed by primary keratinocytes and human epidermoid cell lines. *J Invest Dermatol* 1998; 110(3): 287-91. https://doi.org/10.1046/j.1523-1747.1998.00114.x
47. WANG P, WU P, OHLETH KM, EGAN RW, BILLAH MM: Phosphodiesterase 4B2 is the predominant phosphodiesterase species and undergoes differential regulation of gene expression in human monocytes and neutrophils. *Mol Pharmacol* 1999; 56(1): 170-74. https://doi.org/10.1124/mol.56.1.170
48. LANDELLS LJ, SZILAGY CM, JONES NA *et al*.: Identification and quantification of phosphodiesterase 4 subtypes in CD4 and CD8 lymphocytes from healthy and asthmatic subjects. *Br J Pharmacol* 2001; 133(5): 722-29. https://doi.org/10.1038/sj.bjp.0704120
49. BARBER R, BAILLIE GS, BERGMANN R *et al*.: Differential expression of PDE4 cAMP phosphodiesterase isoforms in inflammatory cells of smokers with COPD, smokers without COPD, and nonsmokers. *Am J Physiol Lung Cell Mol Physiol* 2004; 287(2): L332-43. https://doi.org/10.1152/ajplung.00384.2003
50. PETER D, JIN SL, CONTI M, HATZELMANN A, ZITT C: Differential expression and function of phosphodiesterase 4 (PDE4) subtypes in human primary CD4+ T cells: predominant role of PDE4D. *J Immunol* 2007; 178(8): 4820-31. https://doi.org/10.4049/jimmunol.178.8.4820
51. PULLAMSETTI SS, BANAT GA, SCHMALL A *et al*.: Phosphodiesterase-4 promotes proliferation and angiogenesis of lung cancer by crosstalk with HIF. *Oncogene* 2013; 32(9): 1121-34. https://doi.org/10.1038/onc.2012.136
52. MAURICE DH, KE H, AHMAD F, WANG Y, CHUNG J, MANGANIELLO VC: Advances in targeting cyclic nucleotide phosphodiesterases. *Nat Rev Drug Discov* 2014; 13(4): 290-314. https://doi.org/10.1038/nrd4228
53. LI H, ZUO J, TANG W: Phosphodiesterase-4 inhibitors for the treatment of inflammatory diseases. *Front Pharmacol* 2018; 9: 1048. https://doi.org/10.3389/fphar.2018.01048
54. KWAK HJ, SONG JS, HEO JY, YANG SD, NAM JY, CHEON HG: Roflumilast inhibits lipopolysaccharide-induced inflammatory mediators via suppression of nuclear factor-kappaB, p38 mitogen-activated protein kinase, and c-Jun NH2-terminal kinase activation. *J Pharmacol Exp Ther* 2005; 315(3): 1188-95. https://doi.org/10.1124/jpet.105.092056
55. UDALOV S, DUMITRASCU R, PULLAMSETTI SS *et al*.: Effects of phosphodiesterase 4 inhibition on bleomycin-induced pulmonary fibrosis in mice. *BMC Pulm Med* 2010; 10:26. https://doi.org/10.1186/1471-2466-10-26
56. CORTIJO J, IRANZO A, MILARA X *et al*.:

Roflumilast, a phosphodiesterase 4 inhibitor, alleviates bleomycin-induced lung injury. *Br J Pharmacol* 2009; 156(3): 534-44. https://doi.org/10.1111/j.1476-5381.2008.00041.x
57. PAN JB, HOU YH, ZHANG GJ: Rolipram attenuates bleomycin A5-induced pulmonary fibrosis in rats. *Respirology* 2009; 14(7): 975-82. https://doi.org/10.1111/j.1440-1843.2009.01606.x
58. SISSON TH, CHRISTENSEN PJ, MURAKI Y *et al*.: Phosphodiesterase 4 inhibition reduces lung fibrosis following targeted type II alveolar epithelial cell injury. *Physiol Rep* 2018; 6(12): e13753. https://doi.org/10.14814/phy2.13753
59. SHEPHERD M, MCSORLEY T, OLSEN AE *et al*.: Molecular cloning and subcellular distribution of the novel PDE4B4 cAMP-specific phosphodiesterase isoform. *Biochem J* 2003; 370(Pt 2): 429-38. https://doi.org/10.1042/bj20021082
60. CHEUNG YF, KAN Z, GARRETT-ENGELE P *et al*.: PDE4B5, a novel, super-short, brain-specific cAMP phosphodiesterase-4 variant whose isoform-specifying N-terminal region is identical to that of cAMP phosphodiesterase-4D6 (PDE4D6). *J Pharmacol Exp Ther* 2007; 322(2): 600-9. https://doi.org/10.1124/jpet.107.122218
61. WAN Q, XU C, ZHU L *et al*.: Targeting PDE4B (phosphodiesterase-4 subtype B) for cardio protection in acute myocardial infarction via neutrophils and microcirculation. *Circ Res* 2022; 131(5): 442-55. https://doi.org/10.1161/circresaha.122.321365
62. SMITH PG, WANG F, WILKINSON KN *et al*.: The phosphodiesterase PDE4B limits cAMP-associated PI3K/AKT-dependent apoptosis in diffuse large B-cell lymphoma. *Blood* 2005; 105(1): 308-16. https://doi.org/10.1182/blood-2004-01-0240
63. JIN SL, CONTI M: Induction of the cyclic nucleotide phosphodiesterase PDE4B is essential for LPS-activated TNF-alpha responses. *Proc Natl Acad Sci USA* 2002; 99(11): 7628-33. https://doi.org/10.1073/pnas.122041599
64. JIN SL, LAN L, ZOUDILOVA M, CONTI M: Specific role of phosphodiesterase 4B in lipopolysaccharide-induced signaling in mouse macrophages. *J Immunol* 2005; 175(3): 1523-31. https://doi.org/10.4049/jimmunol.175.3.1523
65. JIN SL, GOYA S, NAKAE S, WANG D, BRUSS M, HOU C *et al*.: Phosphodiesterase 4B is essential for T(H)2-cell function and development of airway hyperresponsiveness in allergic asthma. *J Allergy Clin Immunol* 2010; 126(2): 1252-9.e12. https://doi.org/10.1016/j.jaci.2010.08.014
66. SELIGE J, HATZELMANN A, DUNKERN T: The differential impact of PDE4 subtypes in human lung fibroblasts on cytokine-induced proliferation and myofibroblast conversion. *J Cell Physiol* 2011; 226(8): 1970-80. https://doi.org/10.1002/jcp.22529
67. CILLI A, BAL H, GUNEN H: Efficacy and safety profile of roflumilast in a real-world experience. *J Thorac Dis* 2019; 11(4): 1100-5. https://doi.org/10.21037/jtd.2019.04.49
68. KAVANAUGH A, GLADMAN DD, EDWARDS CJ *et al*.: Long-term experience with apremilast in patients with psoriatic arthritis: 5-year results from a PALACE 1-3 pooled analysis. *Arthritis Res Ther* 2019;21(1): 118. https://doi.org/10.1186/s13075-019-1901-3
69. ROBICHAUD A, STAMATIOU PB, JIN SL *et al*.: Deletion of phosphodiesterase 4D in mice shortens alpha(2)-adrenoceptor-mediated anesthesia, a behavioral correlate of emesis. *J Clin Invest* 2002; 110(7): 1045-52. https://doi.org/10.1172/jci15506.
70. LAMONTAGNE S, MEADOWS E, LUK P *et al*.: Localization of phosphodiesterase-4 isoforms in the medulla and nodose ganglion of the squirrel monkey. *Brain Res* 2001; 920(1-2): 84-96. https://doi.org/10.1016/s0006-8993(01)03023-2
71. 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. https://doi.org/10.3389/fphar.2022.838449
72. REININGER D, HERRMANN FE, NICKOLAUS P *et al*.: PDE4B inhibitor BI 1015550 improves lung fibrosis, modulates transcriptome in bleomycin-treated rats, and attenuates fibrotic markers in human lung fibroblasts and epithelial cells. Poster at European Respiratory Society International Congress, 2023: https://www.globalmedcomms.com/respiratory/ers2023/reininger
73. RICHELDI L, ROY J, SCHMID R, HESSLINGER C, MAHER TM: Effect of BI 1015550, a preferential PDE4B inhibitor, on gene expression profiles and lung function in IPF. Poster at European Respiratory Society International Congress, 2023: https://www.globalmedcomms.com/respiratory/ers2023/richeldi
74. MAHER TM, SCHLECKER C, LUEDTKE D, BOSSERT S, ZOZ DF, SCHULTZ A: Phase I studies of BI 1015550, a preferential phosphodiesterase 4B inhibitor, in healthy males and patients with idiopathic pulmonary fibrosis. *ERJ Open Res* 2022; 8(4): 00240-2022. https://doi.org/10.1183/23120541.00240-2022
75. 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(23): 2178-87. https://doi.org/10.1056/nejmoa2201737
76. COTTIN V, AZUMA A, MAHER TM *et al*.: Effect of BI 1015550, a preferential PDE4B inhibitor, on FEV_1/FVC ratio in idiopathic pulmonary fibrosis. Poster at European Respiratory Society International Congress, 2023: https://www.globalmedcomms.com/respiratory/ers2023/cottin
77. RICHELDI L, AZUMA A, COTTIN V *et al*.: Additive effect of BI 1015550 and nintedanib in patients with IPF. Poster at European Respiratory Society International Congress, 2022: https://www.globalmedcomms.com/respiratory/ers2022/richeldi1
78. MAHER TM, ASSASSI S, AZUMA A *et al*.: Design of a phase III, double-blind, randomised, placebo-controlled trial of BI 1015550 in patients with progressive pulmonary fibrosis (FIBRONEER-ILD). *BMJ Open Respir Res* 2023; 10(1): e001580. https://doi.org/10.1136/bmjresp-2022-001580
79. SWIGRIS J, CUTTS K, MALE N, BALDWIN M, ROHR KB, BUSHNELL DM: The Living with Pulmonary Fibrosis questionnaire in progressive fibrosing interstitial lung disease. *ERJ Open Res* 2021; 7(2): 00145-2020. https://doi.org/10.1183/23120541.00145-2020
80. RICHELDI L, AZUMA A, COTTIN V *et al*.: Design of a phase III, double-blind, randomised, placebo-controlled trial of BI 1015550 in patients with idiopathic pulmonary fibrosis (FIBRONEER-IPF). *BMJ Open Respir Res* 2023; 10(1): e001563. https://doi.org/10.1136/bmjresp-2022-001563
81. CHINN AM, SALMERÓN C, LEE J, SRIRAM K, RAZ E, INSEL PA: PDE4B is a homeostatic regulator of cyclic AMP in dendritic cells. *Front Pharmacol* 2022; 13: 833832. https://doi.org/10.3389/fphar.2022.833832
82. SIUCIAK JA, MCCARTHY SA, CHAPIN DS, MARTIN AN: Behavioral and neurochemical characterization of mice deficient in the phosphodiesterase-4B (PDE4B) enzyme. *Psychopharmacology* (Berl) 2008; 197(1): 115-26. https://doi.org/10.1007/s00213-007-1014-6
83. ZHANG HT, HUANG Y, MASOOD A *et al*.: Anxiogenic-like behavioral phenotype of mice deficient in phosphodiesterase 4B (PDE4B). *Neuropsychopharmacology* 2008; 33(7): 1611-23. https://doi.org/10.1038/sj.npp.1301537
84. LEROY J, RICHTER W, MIKA D *et al*.: Phosphodiesterase 4B in the cardiac L-type Ca2+ channel complex regulates Ca2+ current and protects against ventricular arrhythmias in mice. *J Clin Invest* 2011; 121(7): 2651-61. https://doi.org/10.1172/JCI44747