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REVIEW

Rationale for phosphodiesterase-4 inhibition as a treatment strategy for interstitial lung diseases associated with rheumatic diseases

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ABSTRACT

Interstitial lung disease (ILD) associated with rheumatoid arthritis or with connective tissue diseases such as systemic sclerosis can be collectively named systemic autoimmune rheumatic disease-associated ILDs (SARD-ILDs) or rheumatic musculoskeletal disorder-associated ILDs. SARD-ILDs result in substantial morbidity and mortality, and there is a high medical need for effective therapies that target both fibrotic and inflammatory pathways in SARD-ILD. Phosphodiesterase 4 (PDE4) hydrolyses cyclic AMP, which regulates multiple pathways involved in inflammatory processes. PDE4 is overexpressed in peripheral blood monocytes from patients with inflammatory diseases. However, clinical data on pan-PDE4 inhibition in fibrotic conditions are lacking. The PDE4B subtype is highly expressed in the brain, lungs, heart, skeletal muscle and immune cells. As such, inhibition of PDE4B may be a novel approach for fibrosing ILDs such as idiopathic pulmonary fibrosis (IPF) and SARD-ILD. Preclinical data for PDE4B inhibition have provided initial evidence of both anti-inflammatory and antifibrotic activity, with reduced potential for gastrointestinal toxicity compared with pan-PDE4 inhibitors. In a proof-of-concept phase II trial in patients with IPF, nerandomilast (BI 1015550), the only PDE4B inhibitor currently in clinical development, prevented a decline in lung function over 12 weeks compared with placebo. The potential clinical benefit of PDE4B inhibition is now being investigated in the phase III setting, with two trials evaluating nerandomilast in patients with IPF (FIBRONEER-IPF) or with progressive pulmonary fibrosis other than IPF (FIBRONEER-ILD). Here, we review the preclinical and clinical data that provide rationale for PDE4B inhibition as a treatment strategy in patients with SARD-ILD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Interstitial lung disease (ILD) is a relatively common and life-threatening complication of systemic autoimmune rheumatic diseases (SARDs), comprising connective tissue diseases, microscopic polyangiitis and rheumatoid arthritis.
⇒ The pathophysiology of SARD-ILDs has both fibrotic and inflammatory components.
⇒ Despite the use of immunomodulatory and antifibrotic therapies, a high medical need remains.

WHAT THIS PAPER ADDS

⇒ Preferential inhibition of phosphodiesterase 4B (PDE4B) is a novel approach, with both antifibrotic and anti-inflammatory activity.
⇒ While pan-PDE4 inhibitors are available in other indications, specific PDE4B inhibition reduces gastrointestinal toxicity, enabling higher dosing and may preferentially target the lungs.

HOW THESE FINDINGS MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Preclinical and clinical data of the PDE4B inhibitor nerandomilast suggest that PDE4B inhibition may provide a novel, possibly superior, treatment strategy for patients with SARD-ILDs.

INTRODUCTION

Connective tissue diseases (CTDs) are a heterogeneous group of mostly rare multiorgan systemic autoimmune diseases that include inflammatory idiopathic myopathies (IIMs), Sjögren's disease, systemic sclerosis (SSc), mixed CTD (MCTD) and systemic lupus erythematosus.[1 2] Rheumatoid arthritis (RA), the most common autoimmune arthritis, is a systemic autoimmune disease in which polyarthritis is the leading clinical manifestation. Interstitial lung disease (ILD) associated with CTD (CTD-ILD), RA (RA-ILD) and a few other systemic autoimmune diseases such as microscopic polyangiitis have been collectively named systemic autoimmune rheumatic disease-associated ILDs (SARD-ILDs)[3] or rheumatic musculoskeletal disorder ILDs. SARD-ILDs may be predominantly inflammatory, predominantly fibrotic, or a mixture of both, and are a leading cause of morbidity and mortality for patients with SARDs.[4] The published prevalence rates of SARD-ILDs vary

Table 1 Reported frequency of ILD by disease subtype in a systematic review[8] and cohort studies[9 10]

Disease	Reported prevalence range in registry/multicentre studies (%)*
RA[8]	1–7 (up to 40% subclinical ILD)
SSc[8]	48–54
IIM[9]†	25–50
Antisynthetase syndrome[10]	Up to 75
Sjögren's[8]	4–19
MCTD[8]	40

*Prevalence data are shown as a percentage of study populations using only data from registry (SSc) or multicentre studies (other conditions) reported in the cited publications. The overall prevalence range reported in the publication may be different as it includes single-centre studies.
†Highly dependent on the autoantibodies.
IIM, inflammatory idiopathic myopathy; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; RA, rheumatoid arthritis; SSc, systemic sclerosis.

widely by disease, likely at least partly due to differences in screening and diagnostic methods, as well as reporting and rates of referral to specialised centres. The highest incidence of ILD has been reported among patients with IIMs, MCTD and SSc.[5 6] The reported frequency of ILD in RA varies widely, depending on the population and diagnostic method.[7] However, RA-ILD is one of the most commonly observed SARD-ILDs due to the high number of patients with RA compared with other autoimmune rheumatic conditions. Table 1 shows the estimated frequency of ILD in a range of SARD-ILDs, based on a recent systematic review[8] and cohort studies in IIM/antisynthetase syndrome.[9 10] However, the evidence levels for these estimates are highly variable, and while the frequency of ILD in SSc is derived from relatively robust studies, evidence in other disorders is weak and the frequency of ILD in patients with RA has also been reported at much higher levels than given in the table.[11]

Established therapies for SARD-ILD are largely based on immunosuppressive treatments such as mycophenolate, cyclophosphamide and glucocorticoids, although this may vary according to the underlying disease.[3 12] Tocilizumab (an anti-interleukin (IL)-6 receptor antibody) is approved for the treatment of SSc-ILD in the USA, and rituximab (an anti-CD20 antibody) is approved for SSc in Japan, following positive data from the phase III FocuSSced and DESIRES trials, respectively.[13 14] The non-immunosuppressive antifibrotic medications nintedanib and pirfenidone, originally developed for idiopathic pulmonary fibrosis (IPF), have also been evaluated in SARD-ILDs. Nintedanib is approved in SSc-ILD, based on the phase III Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) trial,[15] and in other chronic fibrosing ILDs with a progressive phenotype, including SARD-ILDs, based on the phase III INBUILD trial.[16 17] Prespecified analyses of INBUILD have demonstrated that the efficacy of nintedanib was consistent across subgroups of patients with autoimmune ILDs,[18 19] although the number of patients in these subgroups was relatively small.[20] Pirfenidone has also shown evidence of activity in the phase II TRAIL1 trial in patients with RA-ILD, where it slowed the rate of decline of forced vital capacity (FVC); however, the trial was underpowered and failed to meet its composite primary endpoint.[21]

Despite advances in the treatments for SARD-ILDs, there remains a high medical need for effective therapies that target both the fibrotic and inflammatory pathways in SARD-ILDs, as well as treatments for extrapulmonary manifestations.

PULMONARY FIBROSIS IN SARD-ILDS

Historically, ILDs have been grouped according to histology, with different diseases showing different patterns of inflammation and fibrosis. IPF, the archetypal progressive fibrosing ILD, has a usual interstitial pneumonia (UIP) histology.[22] Apart from IPF, other ILDs with a frequently reported UIP pattern include chronic hypersensitivity pneumonitis,[23] RA-ILD[24] and antineutrophil cytoplasmic antibodies-associated ILD.[25] A UIP pattern is often associated with progression. However, other patterns and histologies, more frequently seen in ILDs associated with SSc, IIM, Sjögren's disease or MCTD,[26] may also become progressive. Thus, a varying proportion of patients with SARD-ILDs exhibit progressive ILD. The long-term course of progression can be variable, but is generally associated with increased mortality.[27] The pathophysiological mechanisms driving progressive fibrosis in IPF have been extensively investigated in in vivo and in vitro studies (reviewed by Spagnolo *et al*).[28] In SARD-ILD, where rarity is combined with a wide heterogeneity of underlying causes, data are much more sparse. Both further studies based on international collaborations and dedicated multicentre drug trials are required to understand the mechanisms of inflammation and fibrosis and optimal treatment strategies in SARD-ILD. Nevertheless, it has been proposed that the mechanisms of progressive fibrosis are similar between IPF and other forms of progressive pulmonary fibrosis.[29] While experimental proof for this hypothesis is still lacking for most mechanisms, it provides the rationale for the evaluation of established treatments approved for IPF in other progressive fibrosing ILDs.

PHOSPHODIESTERASE (PDE) 4 INHIBITION IN THE TREATMENT OF FIBROSIS

PDEs are a group of enzymes that hydrolyse cyclic guanosine monophosphate (cGMP) and cyclic AMP (cAMP) during intracellular signalling.[30 31] The PDE superfamily includes 11 gene families (PDE1–11), with multiple subtypes within most families (PDE1A, 1B, etc) and further variants of some subtypes (PDE1A1, 1A2, etc). PDE1–3, 10 and 11 hydrolyse both cAMP and cGMP,

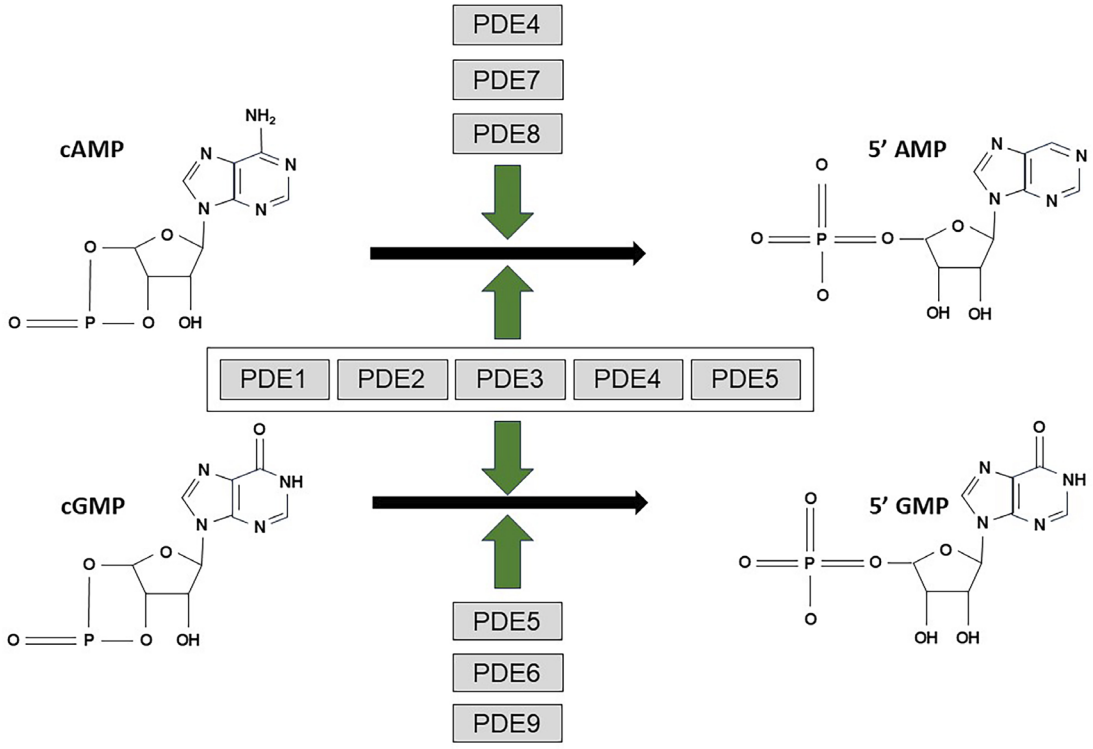

Figure 1 PDE substrate specificity. PDE4, 7 and 8 hydrolyse cAMP; PDE5, 6 and 9 hydrolyse cGMP; PDE1–3, 10 and 11 hydrolyse both cAMP and cGMP. cAMP, 3',5'-cyclic AMP; cGMP, 3',5'-cyclic guanosine monophosphate; PDE, phosphodiesterase.

whereas PDE4, 7 and 8 are specific for cAMP, and PDE5, 6 and 9 hydrolyse cGMP (figure 1).[30–33] Proinflammatory cytokines such as transforming growth factor beta (TGFβ), tumour necrosis factor alpha (TNFα), IL-1, IL-6 and others have been shown to be involved in many inflammatory diseases, including SARD-ILDs.[7 34] A regulator of inflammatory cytokine production, PDE4, has been shown to be overexpressed in peripheral blood monocytes from patients with inflammatory diseases, including psoriasis, psoriatic arthritis, Crohn's disease and systemic lupus erythematosus.[35] Whether PDE4 is overexpressed in mesenchymal cells from patients with fibrotic diseases, however, remains to be determined. Unsurprisingly, PDE4 has been a target for pharmaceutical intervention in several inflammatory diseases, including asthma and chronic obstructive pulmonary disease (COPD), as well as psoriasis, psoriatic arthritis, ankylosing spondylitis, Behçet's disease, atopic dermatitis, inflammatory bowel diseases, RA, lupus erythematosus and neuroinflammation.[36 37] Three pan-PDE4 inhibitors (ie, drugs that do not preferentially inhibit any PDE4 subtype) have been approved for treatment, including roflumilast for severe COPD,[38] apremilast for psoriasis, psoriatic arthritis and oral ulcers associated with Behçet's disease,[39] and topical crisaborole for mild-to-moderate atopic dermatitis.[40]

Preclinical studies have suggested that PDE4 inhibitors reduce or prevent inflammation-driven fibrosis. The PDE4 inhibitor rolipram inhibited lung fibrosis in inhaled bleomycin-challenged mice and rats.[41] Similarly, roflumilast inhibited histologically assessed fibrosis and fibrosis-associated serum markers in a bleomycin mouse model of lung fibrosis[42]; it also inhibited fibrosis and collagen deposition in a mouse model of graft-versus-host disease.[43] In addition, there is evidence for possible direct antifibrotic effects of PDE4 inhibition. PDE4 inhibitors have been shown to inhibit fibrosis and/or fibrotic markers in preclinical studies in tissues other than the lung. These include the skin, where rolipram and apremilast reduced the activity of macrophages and release of fibrotic cytokines,[44] kidneys, where rolipram replenished cAMP levels and inhibited extracellular matrix (ECM) deposition in fibrotic kidney tissue,[45] and liver, where roflumilast normalised levels of fibrotic cytokines in rats with chemically induced liver fibrosis.[46] The full mechanism by which PDE4 inhibits fibrosis is not completely understood, but in vivo it is believed to also involve inhibition of myofibroblast transformation and proliferation, and expression of ECM proteins, in addition to effects on inflammatory cells, including macrophages and monocytes.[36] As shown in figure 2, PDE4 acts via 5'-AMP in monocytes, macrophages and fibroblasts, to increase the release of proinflammatory cytokine and cellular mediators. Additionally, in monocytes and macrophages, PDE4 degrades cAMP, promoting proinflammatory cytokine and downregulating anti-inflammatory cytokine release, whereas in fibroblasts the degradation of cAMP by PDE4 increases ECM synthesis, fibroblast proliferation and myofibroblast differentiation. Conversely, inhibition of PDE4, using either pan or preferential PDE4 subtype inhibition, prevents the degradation of cAMP

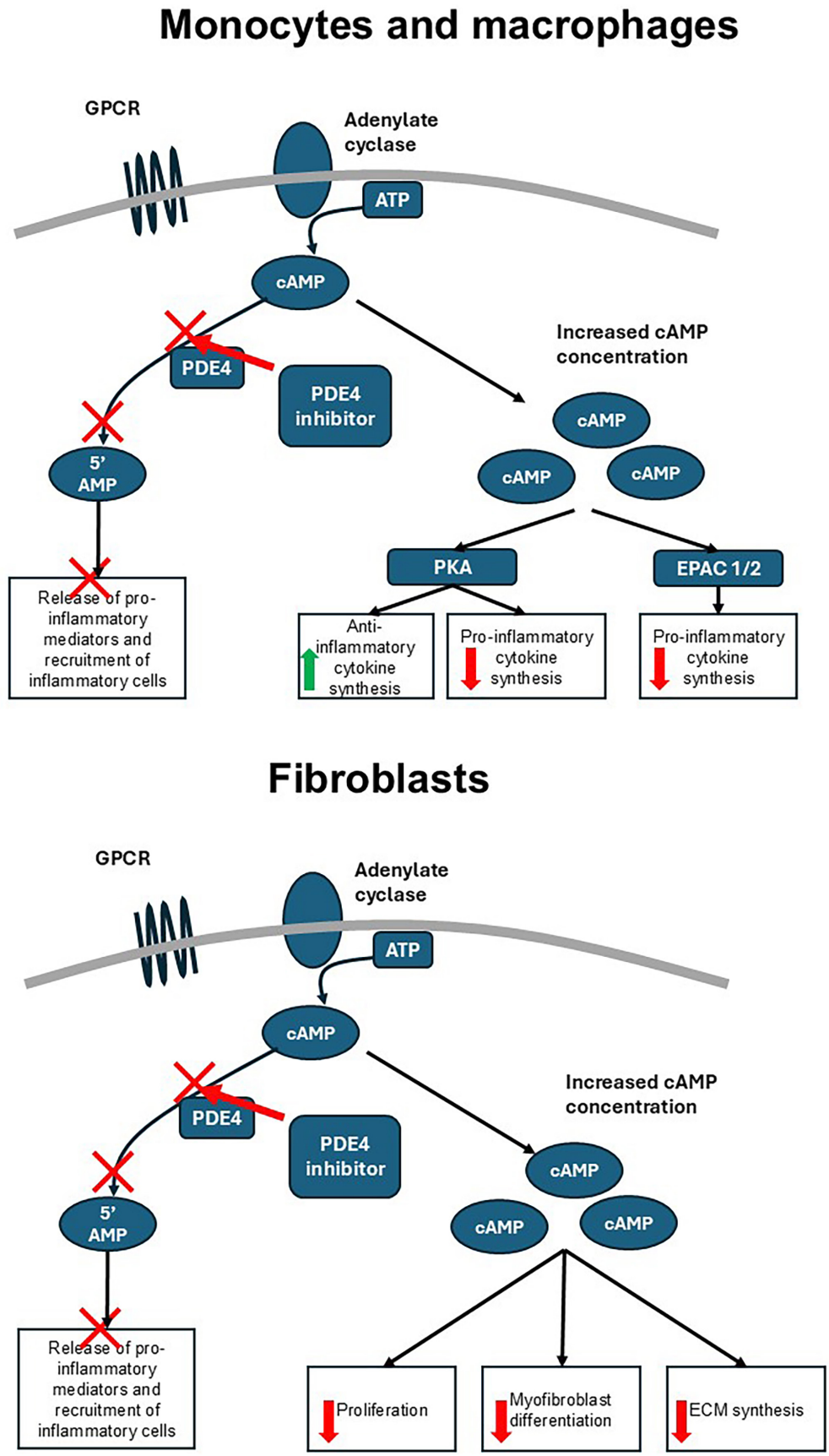

Figure 2 Proposed mechanisms of anti-inflammatory and antifibrotic activity associated with PDE4 inhibition (based on Kolb *et al*).[36] Preferential PDE4B inhibition may target this activity to the lung. cAMP, cyclic AMP; ECM, extracellular matrix; EPAC1/2, exchange protein directly activated by cAMP 1/2; GPCR, G protein-coupled receptor; PDE, phosphodiesterase; PKA, protein kinase A.

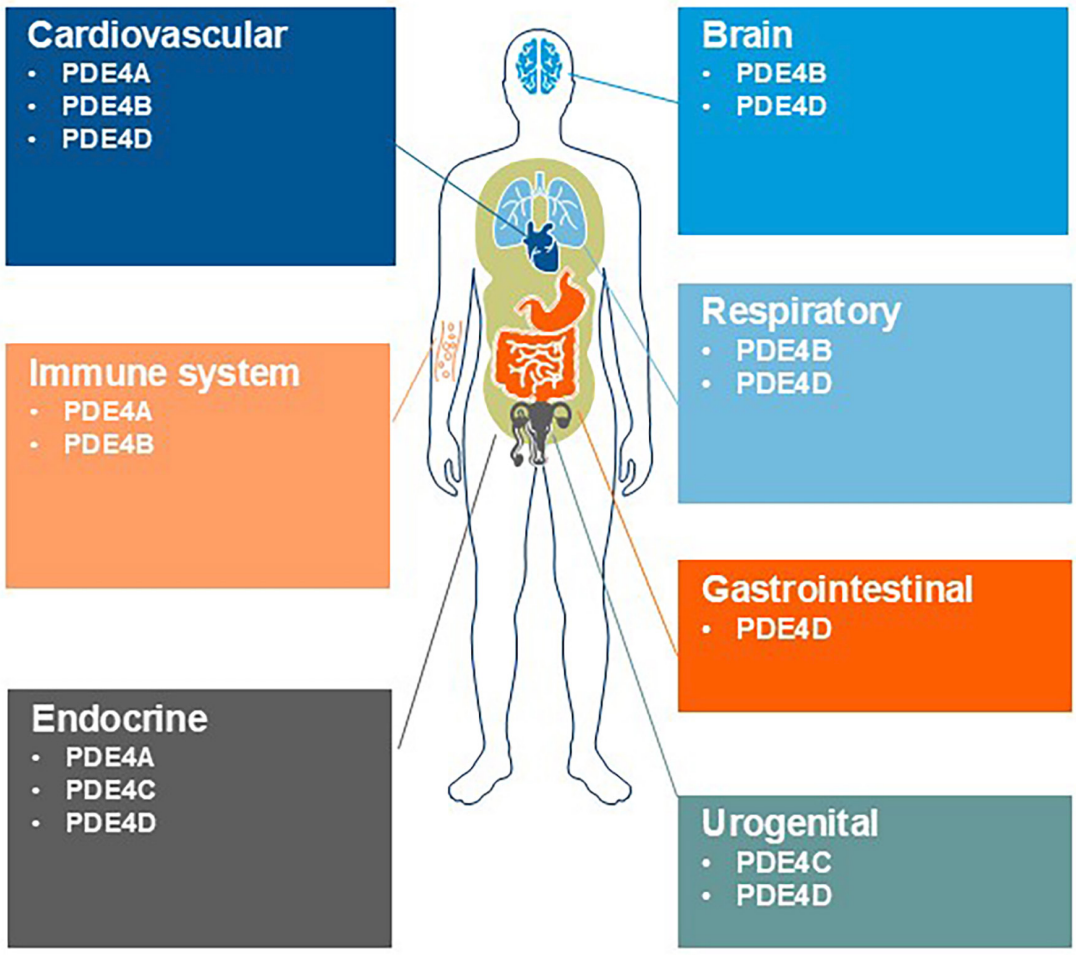

Figure 3 PDE4 expression in different tissues.[36] PDE, phosphodiesterase.

in monocytes, macrophages and fibroblasts.[36] Increased cAMP in monocytes and macrophages enhances anti-inflammatory cytokine synthesis and reduces proinflammatory cytokine synthesis, whereas in fibroblasts it is hypothesised to reduce ECM synthesis, fibroblast proliferation and myofibroblast differentiation.[36 47] However, clinical data on pan-PDE4 inhibition in fibrotic conditions are lacking.

PREFERENTIAL INHIBITION OF PDE4B

Differential expression of PDE subtypes/families across different tissues and cell types allows pharmacological targeting in different diseases.[36] PDE4 is involved in inflammatory signalling and is widely distributed, but the PDE4B subtype has high expression in brain, lung and immune cells, as well as heart and skeletal muscle (figure 3).[30 36] With high expression of PDE4B in the lungs, preferential inhibition of this subtype may offer the possibility of selectively inhibiting lung fibrosis with reduced adverse effects in other tissues. For example, PDE4D, but not PDE4B, is believed to be the subtype responsible for the nausea and emesis (vomiting) associated with pan-PDE4 inhibitors, due to differential activity on adrenoceptor signalling.[48]

Preclinical data

Nerandomilast (BI 1015550) is a preferential PDE4B inhibitor and is the only one currently in clinical development, to our knowledge. Nerandomilast is approximately nine times more potent in vitro for inhibition of recombinant PDE4B compared with PDE4D,[47] suggesting that it may be used at higher effective doses than pan-PDE4 inhibitors. Nerandomilast has both anti-inflammatory and antifibrotic effects. In vitro, nerandomilast inhibited the release of proinflammatory cytokines (TNFα and IL-2) in human and rat whole blood and/or peripheral blood mononuclear cells. Potent anti-inflammatory activity was also shown by the ex vivo inhibition of TNFα synthesis in two well-known mouse models of lung fibrosis (induced either by bleomycin or silica), and by the inhibition of neutrophil influx into bronchoalveolar lavage fluid in *Suncus murinus*,[47] a house shrew that is phylogenetically closer to primates than rodents and is particularly sensitive to emesis induction.[49] The inflammation-dependent antifibrotic effects of nerandomilast were shown in vivo by improved lung function parameters and reduced fibrosis in the bleomycin and silica murine models of fibrosis, with significant differences in FVC and pulmonary pressure volume in the bleomycin model. These in

vivo data were supported by in vitro data showing antifibrotic effects. Nerandomilast mediated the inhibition of the profibrotic activity of primary lung fibroblasts from patients with IPF.[47] TGFβ-stimulated myofibroblast transformation was inhibited, as was basic fibroblast growth factor plus IL-1β-induced cell proliferation, and the expression of various ECM proteins was reduced.[47] Interestingly, when added to nerandomilast, nintedanib showed an approximately tenfold synergistic inhibitory effect on the proliferation of primary lung fibroblasts from patients with IPF, and an additive effect on the expression of collagen 1A1. No additive effects were seen on the expression of collagen 3A1 or fibronectin.[47] In *S. murinus*, nerandomilast also showed less potential to induce emesis compared with the pan-PDE4 inhibitor roflumilast.[47]

Clinical data

Nerandomilast was first evaluated in a phase I study in healthy individuals and a phase Ic study in patients with IPF, in which it showed an acceptable tolerability profile.[50] The efficacy and safety of nerandomilast were subsequently investigated in a placebo-controlled, randomised (2:1) phase II study in 147 patients with IPF receiving or not receiving a stable dose of pirfenidone/nintedanib background treatment for at least 8 weeks before screening.[51] Nerandomilast prevented lung function decline over 12 weeks in patients with and without background antifibrotic use compared with placebo: median change in FVC was +2.7 mL (95% credible interval (CI) −38.2 to 38.2) vs −59.2 mL (95% CI −111.8 to −17.9) in patients with background antifibrotic use; in those without background antifibrotic use it was +5.7 mL (95% CI −39.1 to 50.5) vs −81.7 mL (95% CI −133.5 to −44.8).[51] The median difference in patients with or without background antifibrotic use compared with placebo was 62.4 mL (95% CI 6.3 to 125.5) and 88.4 mL (95% CI 29.5 to 154.2), respectively, with the probability of nerandomilast being superior to placebo being 0.986 and 0.998, respectively (exceeding the treatment effect probability of 0.75).[51] Nerandomilast had an acceptable safety profile, with mild-to-moderate diarrhoea the most common adverse event (more frequent in patients receiving background antifibrotics), and few patients reporting nausea/vomiting.[51] Severe gastrointestinal (GI) effects have been reported with pan-PDE4 inhibitors. For example, apremilast can cause diarrhoea, nausea and vomiting events (some requiring hospitalisation), which may require apremilast discontinuation, and this has resulted in a warning/precaution on the label.[39] Gradual dose escalation may improve tolerability. Improved GI side effects are particularly important for SARD-ILDs; while the GI side effect profile appears promising with nerandomilast, the phase II study was only 12 weeks in duration. These promising results in phase II warranted further investigation, and nerandomilast is currently being evaluated over 52 weeks in two phase III, placebo-controlled trials in more than 1000 patients with IPF (FIBRONEER-IPF, NCT05321069[52]) and in a similar number of patients with other progressive fibrosing ILDs (FIBRONEER-ILD, NCT05321082[53]). The trials will address longer-term efficacy and safety of nerandomilast. Both trials include patients receiving and not receiving background antifibrotic therapy. In the phase II trial, patients receiving nerandomilast who were on background antifibrotic therapy had a higher incidence of diarrhoea than those not on antifibrotics (31% vs 17%) and were more likely to discontinue treatment due to diarrhoea (6% vs 0%).[51] It will therefore be important to fully establish the GI tolerability of nerandomilast in combination with antifibrotic therapy in these phase III studies. Another important consideration is the role of PDE4B in the brain. PDE4B plays a major role in brain signalling and has been implicated in cognitive function, memory and psychiatric disorders and neuroinflammation.[54] A low risk of psychiatric events was observed in studies of the pan-PDE4 inhibitor apremilast.[55] The FIBRONEER trials will also therefore assess psychiatric events as events of special interest. Both of these trials have completed recruitment with results expected in 2025.

CONCLUSIONS

Inhibition of PDE4B has been shown to reduce inflammatory markers and inflammation-driven fibrosis in in vitro and animal studies, with evidence of direct antifibrotic effects on fibroblasts from patients with IPF in vitro. In a phase II clinical trial, the PDE4B inhibitor nerandomilast stabilised lung function over 12 weeks in patients with IPF. The available data suggest that preferential PDE4B inhibition is a promising strategy in the treatment of SARD-ILD.

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