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Promising Idiopathic Pulmonary Fibrosis Therapeutics

M. O'Callaghan[1,2], C. McCarthy[1,2], M.P. Keane[1,2]

1. Department of Respiratory Medicine, St. Vincent's University Hospital, Dublin 4, Ireland.
2. School of Medicine, University College Dublin, Dublin 4, Ireland.

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic lung disease, with a median survival of 3-5 years, and it is the archetypal form of fibrotic interstitial lung disease (ILD).[1] Until 2012, the standard treatment regimen for IPF involved immunosuppression with corticosteroids and azathioprine and anti-oxidants such as N-acetylcysteine (NAC) to preserve lung function. The results of the PANTHER-IPF study were published that year and reported increased mortality and hospitalisation in patients taking this combination of therapy compared to patients receiving placebo alone.[2] A move away from immunosuppression and NAC resulted and there were no apparent effective treatment options. In the last decade considerable advances have been made with two anti-fibrotic therapies now available, pirfenidone and nintedanib.[3]

Pirfenidone is an orally administered pyridine with anti-inflammatory, antioxidant, and anti-fibrotic effects. The precise mechanism of these actions remains unknown, but it regulates the expression of TGF-β and inhibits fibroblast and collagen synthesis.[4] In clinical trials pirfenidone led to a significant reduction in disease progression.[5] Nintedanib is a tyrosine kinase inhibitor which targets PDGF receptors, VEGF receptors and FGF receptors.[6] In clinical trial data nintedanib has led to a significant reduction in the rate of FVC decline over a 52-week period and significantly fewer patients suffered a 5% or 10% decline in FVC with nintedanib versus placebo.[6] These promising clinical trial results have been echoed by the real-world data.[7] Adverse events are common for both anti-fibrotic agents but they remain well tolerated especially if support to manage side effects is provided.[8]

Richeldi et al performed a multi-centre randomised double-blind place-controlled phase 2 trial where the efficacy and safety of the oral preferential inhibitor of the phosphodiesterase 4B (PDE4B) subtype, BI 1015559, was evaluated in patients with IPF. Anti-inflammatory and anti-fibrotic properties have previously been attributed to PDE4 inhibition, and inhibition of the PDE4B subtype was chosen to minimise adverse effects. Patients were grouped into those on anti-fibrotic therapy and those who weren't and then were randomised in a 2:1 fashion to BI 1015559 18mg orally twice daily or placebo. The primary end point was change in FVC from baseline after 12 weeks.[9]

97 patients were randomised to the treatment group; 48 of whom were on background anti-fibrotic therapy with 15 patients discontinuing the drug prematurely due to adverse effects. Gastrointestinal disorders were the most commonly reported adverse effect, reported in 27% of patients in the treatment group and 16% of those in the placebo group. Incidence was higher in patients on background anti-fibrotic therapy. With respect to treatment efficacy, there was a 5.7ml change in FVC in the BI 1015550 group and a –81.7 ml change in the placebo group among patients without background anti-fibrotic use (median difference, 88.4 ml; 95% credible interval, 29.5 to 154.2; probability that BI 1015550 was superior to placebo, 0.998). Where patients were already taking anti-fibrotics, the respective FVC changes were 2.7 ml and –59.2 ml (median difference, 62.4 ml; 95% credible interval, 6.3 to 125.5; probability that BI 1015550 was superior to placebo, 0.986).[9]

This trial demonstrates stability in FVC with PDE4B inhibition regardless of background anti-fibrotic treatment and paves the way for larger phase 3 trials. While adverse effects were common, BI 1015559 overall has an acceptable safety profile in this study. Even allowing for the phase 2 nature of this study and the rare nature of IPF, the sample size was small, and the trial ran for just 12 short weeks. Longer studies with larger numbers are needed for validation.

Phosphodiesterases (PDEs) facilitate the hydrolysis of cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP). The inhibition of PDE4 can elevate the intracellular level of cAMP and subsequently modulate inflammation and immunological responses. This has led to the development of therapies targeting PDE4 and subsequent introduction into clinical practice in the last decade. Oral roflumilast is approved for patients with severe chronic obstructive pulmonary disease (COPD) to reduce exacerbations, apremilast is approved for treatment of psoriatic arthritis and plaque psoriasis, crisaborole is effective in the treatment of atopic dermatitis and ibudilast for Krabbe disease.[10, 11]

While these drugs and their efficacy both in clinical trial and clinical practice settings are impressive, the various adverse effects are their primary issue, limiting widespread use and applicability. Emesis in particular has been a major challenge, and recent studies suggest that PDE4D activity, but not PDE4B, could modulate the activity of α2-adrenoceptor, and thus is most likely responsible for emesis and other side effects.[11] This led to the development of drugs like BI 1015559 that should have improved tolerance and safety.[9]

In the past decade, PDE4 inhibitors have also garnered attention because of animal and human studies demonstrating a potential role in fibrosis.[10, 12] In murine bleomycin induced fibrosis models, PDE4 inhibitors ameliorated the degree of fibrosis and inhibited a range of pro-fibrotic markers.[12] In normal human lung fibroblasts, TGF-β induced transition to myofibroblasts was inhibited by PDE4 inhibitor in the presence of PGE_2 as measured by α-SMA protein expression. Another group demonstrated a reduction in TGF-β induced type 1 collagen mRNA expression when normal human lung fibroblasts were exposed to two other PDE4 inhibitors.[10] These studies are only a sample of the extensive studies done to date in this field, all supporting the anti-fibrotic properties of PDE4 inhibitors.

Despite the current available treatments, mortality for patients with IPF remains high with an overall 3-year and 5-year cumulative survival of 61.8% and 45.6% in a recent systematic review.[13] Lung transplantation is the only potentially curative treatment for patients with IPF.[10] Thus new therapies are very much needed. This study, albeit low powered, shows promising early data for the role of PDE4B inhibitors in IPF. Unlike pirfenidone and nintedanib, PDE4B inhibitors appear to not only slow fibrotic disease progression but prevent disease progression entirely. Future studies will be needed to ascertain the widespread applicability, tolerance, and efficacy of this treatment.

Corresponding Author:
Marissa O'Callaghan
Respiratory SpR and Special lecturer in medicine,
UCD School of Medicine,
Education and Research Centre,
St. Vincent's University Hospital,
Elm Park,
Dublin 4.
E-Mail: Marissa.ocallaghan1@ucd.ie

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