Respiratory Medicine 131 (2017) 49–57

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Review article

Therapeutic targets in idiopathic pulmonary fibrosis

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ARTICLE INFO

Article history:
Received 14 December 2016
Received in revised form
10 July 2017
Accepted 31 July 2017
Available online 1 August 2017

Keywords:
Idiopathic pulmonary fibrosis

ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a progressive and ultimately fatal interstitial lung disease. After many drugs failed in clinical trials, improvements in the understanding of the pathogenesis of IPF led to the approval of two drugs that slow the progression of the disease. However, the prognosis for patients with IPF remains poor and the search continues for drugs that inhibit the pathogenic pathways active in IPF to reduce or even halt the progression of the disease. In this article, we review the mechanisms of action of the two approved therapies for IPF (nintedanib and pirfenidone) and of the investigational compounds that are in Phase II trials and discuss the potential for combination therapy in the treatment of IPF.

Contents

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http://dx.doi.org/10.1016/j.rmed.2017.07.062
0954-6111/

1. Introduction

IPF is a progressive fibrosing interstitial lung disease with a median survival time from diagnosis of 2–3 years [1]. Although rare, the worldwide incidence of IPF is similar to that of several malignancies, including hepatic, testicular and cervical cancers, and appears to be increasing [2]. IPF is primarily a disease of the elderly, with the vast majority of cases being diagnosed in individuals over 60 years of age [3]. IPF is associated with chronic dyspnoea, cough, declining lung function, and impairments in patients' quality of life [1,4].

2. Pathogenesis of IPF

Formerly regarded as a result of chronic inflammation, the current hypothesis for the pathogenesis of IPF is one of aberrant wound healing in response to repeated alveolar epithelial cell (AEC) micro-injury in genetically susceptible individuals [5–7]. The triggers for this aberrant response are poorly understood, but may include cigarette smoke, virus or aspiration of gastric acid [6,8,9].

During the normal wound healing process, inflammatory cells are attracted to the site of injury and recruit fibroblasts that proliferate and differentiate into myofibroblasts, which deposit extracellular matrix (ECM). Myofibroblasts then undergo apoptosis, there is resorption of the ECM, and epithelial cells migrate to the site of injury, leading to re-epithelialisation and tissue repair [5]. In IPF, aberrant activation of epithelial cells leads to the production of pro-fibrotic mediators that drive fibroblast proliferation and fibroblast to myofibroblast transformation (FMT). Epithelial–mesenchymal transition (EMT), proliferation of interstitial fibroblasts, pericytes and an influx of circulating fibrocytes may contribute to the expansion of myofibroblasts, but their relative contributions are unclear [6,8,9]. Fibroblasts and myofibroblasts show resistance to apoptosis and accumulate at the sites of active fibrosis in fibroblastic foci. Different parts of the lungs reach different stages of the disease process, resulting in a patchy appearance, in which areas of fibrosis occur next to areas of less affected or even healthy tissue [1]. Excessive deposition of ECM by myofibroblasts results in scarring and stiffness, which decrease lung volume [7–9]. In preclinical models of IPF, this mechanical stiffness contributes to the development of pulmonary fibrosis via activation of TGF-β1 [10].

The role of angiogenesis in IPF remains unclear. IPF is associated with heterogeneous microvascular abnormalities, with fibrotic areas having fewer blood vessels and non-fibrotic areas being highly vascularised. It remains unclear whether abnormal vascularization in IPF supports fibroproliferation and inhibition of normal repair mechanisms or is a compensatory mechanism to limit fibrogenesis [11,12].

A multitude of profibrotic mediators and signalling pathways are involved in the pathogenesis of pulmonary fibrosis, of which TGF-β is particularly potent [6,8,9]. Tyrosine kinases have been shown to play a critical role in the pathogenesis of IPF [13]. For example, increased release of platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) are seen in the lungs of patients with IPF and blocking PDGF receptor- or FGF-2 signalling attenuates lung fibrosis in animal models [13]. Due to the multiple pathways involved in the pathogenesis of IPF, multi-target therapies are likely to be most effective [7]. Furthermore, subgroups of patients with IPF with different pathogenetic profiles will likely differ in their responsiveness to particular drugs [14].

3. Mechanisms of action of approved and investigational therapies for IPF

3.1. Pirfenidone

Pirfenidone (Esbriet®; Roche/Genentech USA, Inc) has been approved for the treatment of IPF in several countries and regions including the US and for the treatment of mild to moderate IPF in Europe (e.g. Ref. [15]). In patients with IPF, pirfenidone slows disease progression by reducing decline in forced vital capacity (FVC) with side-effects, mainly related to the gastrointestinal tract and skin, which are tolerated by most patients [16,17].

The mode of action of pirfenidone in the treatment of IPF remains unclear. At concentrations often exceeding the maximum exposure achieved in patients with IPF, pirfenidone reduces markers of oxidative stress [18,19], reduces the proliferation of lung fibroblasts and their differentiation into myofibroblasts by attenuating key TGF-β-induced signalling pathways (i.e., Smad3, p38, and Akt), reduces the expression of TGF-β-induced heat-shock protein 47 (HSP47), which is involved in processing/secretion of procollagen, and reduces expression of α smooth muscle actin (α-SMA) and collagen type I [20–22]. Pirfenidone has been shown to have anti-fibrotic, anti-inflammatory and anti-oxidant properties in animal models of lung fibrosis (Table 1, Fig. 1). In animals with bleomycin-induced pulmonary fibrosis, pirfenidone reduced TGF-β levels, the influx of fibrocytes, the number of myofibroblasts and the accumulation of inflammatory cells [23–25]. Pirfenidone also reduced the accumulation of hydroxyproline (a major component of collagen and marker of fibrosis) and levels of procollagen I and III in these models [23–25].

3.2. Nintedanib

Nintedanib (Ofev®; Boehringer Ingelheim) has been approved for the treatment of IPF in several countries and regions including the US and Europe (e.g. Ref. [26]). Clinical trials have shown that nintedanib slows the rate of decline in FVC and reduces the risk of acute exacerbations in patients with IPF, with side-effects, most commonly diarrhoea, which are manageable for most patients [27–29].

Nintedanib is a potent intracellular inhibitor of the receptor tyrosine kinases PDGFR, FGFR and vascular endothelial growth factor receptor (VEGFR) and non-receptor tyrosine kinases of the Src family [30,31]. Nintedanib attenuates processes that are essential for fibrosis (Table 1, Fig. 1). In human lung fibroblasts, nintedanib inhibited fibroblast proliferation (including migration of fibrocytes and fibrocyte-induced fibroblast proliferation), growth factor-stimulated fibroblast motility and contraction, and TGF-β-induced fibroblast to myofibroblast transformation [31–37]. In addition, nintedanib reduced TGF-β-induced deposition of collagen and upregulated secretion of pro-matrix metalloproteinase 2 while downregulating its inhibitor, suggesting increased degradation of the ECM [31]. In animal models of pulmonary fibrosis, nintedanib has demonstrated anti-fibrotic effects including reductions in lung collagen content and morphometric fibrosis scores and reduced expression of TGF-β and procollagen I [34,35]. Recent data suggest that nintedanib has beneficial effects on the pulmonary microvasculature [38], inhibits migration of fibrocytes [36] and prevents the polarisation of M2 macrophages [39], which are believed to be key mediators of tissue fibrosis [40], in mice treated with bleomycin. Anti-inflammatory effects of nintedanib have been demonstrated by reductions in lymphocytes and neutrophil counts in bronchoalveolar lavage fluid (BALF), reduced inflammatory cytokines

Table 1
Pathogenic mechanisms targeted by drugs that are approved for or in Phase II development for treatment of IPF.

Pathomechanisms in fibrotic lung disease	Nintedanib	Pirfenidone	BMS-986020	TD139	PBI-4050	BG00011	SAR156597	PRM-151	KD025	Tipelukast	GLPG 1690	FG-3019	Lebrikizumab	CC-90001
Epithelial activation and mesenchymal transition	– [35]			○ [42]		○ [65]						○ [83,84]		
Oxidative stress		○ [18]			● [56]									
Inflammatory macrophage activation	● [34]	● [25]	○ [47]	– [42]	● [55]	– [65]		● [66]	● [63]	○ [62]	○ [50]			
Fibroblast proliferation	● [31,33,34,36]	○ [20,21,33]	– [48]	– [42]		○ [65]				○ [63]		○ [84]	– [77]	
Fibroblast migration	● [35]		○ [48]			○ [65]	● [82]	○ [68]	○ [73]	○ [63]		○ [83]		
Fibroblast to myofibroblast transformation (FMT)	○ [34]	○ [20,21,24]	– [48]	○ [42]				○ [69]	○ [74]			○ [83]	○ [77]	○
Fibroblast contraction	● [37]	○ [93,94]												
Fibrocyte function and accumulation	● [36,93]	● [23]	– [48]	– [42]			○ [67]	● [66]					○ [67]	
ECM deposition	○ [31,35]	● [22,23,95]	○ [48]	● [42,44]	● [55]	○ [65]	○ [80]	○ [68]	○ [74]	● [62]	● [51]	● [85]	○ [77,80]	● [90]
Induction of (myo)fibroblast apoptosis			○ [49]						○ [74]					
Reepithelialisation			○ [49]						○ [73]					● [90]
Vascular alterations	● [38]		○ [47,48]						○ [73]			○ [84]		

– no effect (based on direct or indirect evidence); ○ weak or indirect evidence of an effect; ● strong evidence of an effect (based on *in vitro* or *in vivo* data with this specific compound).

and reduced histological inflammation [34].

3.3. Agents in phase II development

A number of agents for the treatment of IPF have been investigated in ongoing or recently completed Phase II trials (Table 2). These agents act on different aspects of the pathogenic processes of IPF (Table 1 and Fig. 1).

3.4. TD139

TD139 (Galecto Biotech/Bristol-Myers Squibb) is an inhaled dry powder galectin-3 inhibitor [41]. Galectin-3 is a β-galactoside binding lectin that regulates the expression of TGF-β receptors on the surface of AECs and is a mediator of TGF-β-induced lung fibrosis [42]. Bleomycin-treated galectin-3 knockout mice show reduced lung fibrosis and lung collagen levels, while AECs and fibroblasts from galectin-3 knockout mice show reduced (myo)fibroblast activation, EMT and collagen I production in response to TGF-β [42]. Galectin-3 levels are elevated in the BALF and serum of patients with IPF [42,43].

When β-catenin moves from the cytoplasm to the nucleus, it mediates the activation of transcription factors, thereby promoting collagen synthesis, and nuclear β-catenin localisation is observed in cells forming fibroblastic foci [42]. TD139 has been shown to reduce TGF-β1–induced β-catenin translocation to the nucleus [42,43]. In mice treated with bleomycin, TD139 reduced β-catenin activation, galectin-3 expression and total lung collagen [42,43]. TD139 also reduced galactin-3 expression in macrophages from the BALF of patients with IPF [43].

In healthy subjects, single doses of TD139 have been shown to be well tolerated with mild adverse events including headache, cough and dose-related paraguesia [41]. In a Phase IIa randomised placebo-controlled study in patients with IPF (N = 24), TD139 0.3 mg, 3 mg and 10 mg once daily for 14 days was well tolerated [44].

3.5. BMS-986020

BMS-986020 (Bristol-Myers Squibb) is an oral antagonist of the lysophosphatidic acid (LPA) receptor 1 (LPA_1) [45]. LPA is a lipid concentrated in the serum that binds to six receptors ($LPA_{1–6}$) involved in cell survival, proliferation, migration, differentiation, vascular regulation and cytokine release [46]. Acting via LPA_1, LPA stimulated fibroblast migration in a bleomycin model of pulmonary fibrosis [47], while mice lacking LPA_1 were protected from fibrosis via attenuation of fibroblast recruitment and vascular leak [48]. LPA signalling also promotes apoptosis of lung epithelial cells and resistance of fibroblasts to apoptosis in animals with bleomycin-induced fibrosis [49]. LPA is increased in the BALF of patients with IPF and inhibition of LPA_1 inhibited fibroblast chemotaxis induced by BALF from patients with IPF [48]. No data on the efficacy or safety of BMS-986020 in humans has been presented.

3.6. GLPG1690

The oral autotaxin (ATX) inhibitor GLPG1690 (Galapagos NV) is another agent targeting LPA. ATX is the enzyme largely responsible for extracellular LPA production, and increased concentrations of ATX have been found in the lungs of patients with IPF and in BALF from mice with experimental fibrosis [50]. In bleomycin mouse models, the genetic deletion of ATX from bronchial epithelial cells

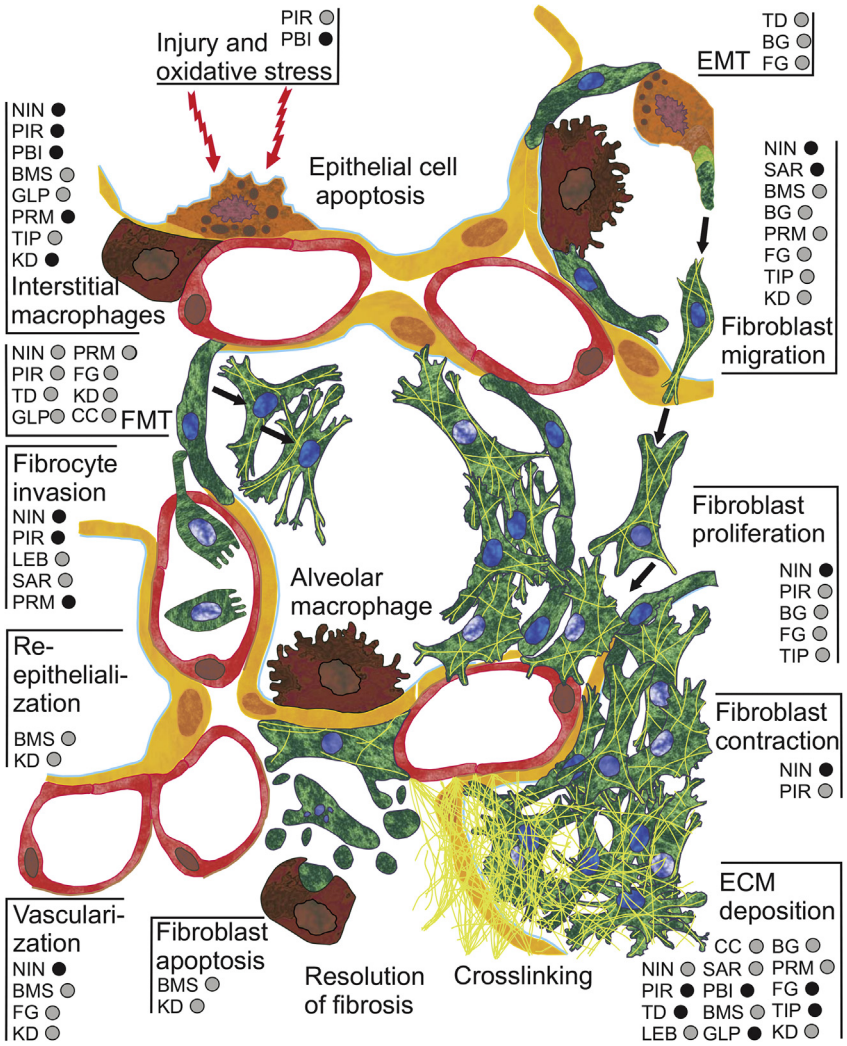

Fig. 1. Current hypotheses for where pharmacological agents act on the pathogenic processes of IPF. In the pathogenesis of IPF, injury and oxidative stress damage epithelial cells, resulting in apoptosis and epithelial to mesenchymal transition (EMT). Interstitial and alveolar macrophages release pro-fibrotic mediators but also clear apoptotic cells to resolve fibrosis. Upon stimulation, fibrocytes invade the lung and resident fibroblasts migrate and proliferate. Fibroblasts transform to myofibroblasts (fibroblast to myofibroblast transition [FMT]), which secrete extracellular matrix (ECM). Excess deposition and cross-linking of ECM components like collagens leads to stiffening of the lung tissue. Vascularization around fibrotic foci is also increased. Reepithelialization helps to repair the fibrotic lung.
Approved drugs for the treatment of IPF:
NIN = nintedanib, PIR = pirfenidone.
Drugs in ongoing or recently completed Phase II trials for the treatment of IPF:
BMS = BMS-986020, BG = BG00011, CC = CC-90001, FG = FG-3019, GLP = GLPG1690, KD = KD025, LEB = lebrikizumab, PBI = PBI-4050, PRM = PRM-151, SAR = SAR156597, TIP = tipelukast, TD = TD139, ● = strong evidence that the pathogenic mechanism is influenced by the drug, ● = weak evidence that the pathogenic mechanism is influenced by the drug.

or macrophages attenuated disease severity and inhibition of ATX reduced the development of pulmonary fibrosis [49]. GLPG1690 is a potent inhibitor of ATX. In GLPG1690-treated mice, there is an inverse relationship between LPA and GLPG1690 plasma levels [51]. In mice with bleomycin-induced pulmonary fibrosis, GLPG1690 reduced collagen content and lung fibrosis [48] and was superior to pirfenidone 50 mg/bid on both of these measures [52]. The safety and tolerability of GLPG1690 have been demonstrated in healthy volunteers [53], but no data has been presented on the safety or efficacy of GLPG1690 in patients with fibrotic lung disease.

3.7. PBI-4050

PBI-4050 (ProMetic Biosciences) is an orally administered small molecule with anti-inflammatory/anti-fibrotic properties. In mice with bleomycin-induced pulmonary fibrosis, PBI-4050 reduced pro-fibrotic/inflammatory cytokines (TGF-β1, monocyte chemoattractant protein-1, connective tissue growth factor [CTGF], interleukin [IL]-23 and IL-6), showed anti-oxidant properties and reduced α-SMA expression, collagen I deposition, fibronectin expression, plasminogen activator inhibitor-1 (PAI-1) expression and fibrosis [54–59]. PBI-4050 reduced CTGF and collagen I expression in TGF-β-stimulated human AECs [59], and expression of CTGF, collagen I, α-SMA and PAI-1 in TGF-β-stimulated human dermal fibroblasts [57,59]. In TGF-β-stimulated human lung fibroblasts, PBI-4050 reduced inflammatory/profibrotic cytokines, growth factors (endothelin 1, epithelial growth factor, PDGFα, VEGF and TGF-β2) and myofibroblasts (α-SMA) [55,59]. The safety and tolerability of PBI-4050 have been demonstrated in healthy volunteers and in patients with type 2 diabetes [60]. In an open-label

Table 2
Products in ongoing or recently completed Phase II trials in patients with IPF.

Agent (company)	Type of molecule	ClinicalTrials.gov identifier	Study design; sample size	Primary endpoint and duration of assessment	Estimated primary completion date[a]
BMS-986020 (Bristol-Myers Squibb)	Lysophosphatidic acid receptor antagonist	NCT01766817	Randomised, placebo-controlled; n = 135	Rate of change in FVC at week 26	Completed April 2016
TD139 (Galecto Biotech [Bristol-Myers Squibb])	Galectin-3 inhibitor	NCT02257177	Randomised, dose escalation, placebo-controlled with dose expansion; n = 60	Adverse events over 2 weeks	Completed December 2016
PBI-4050 (ProMetic BioSciences, Inc.)	Inhibitor of CTGF, α-SMA and collagen I expression	NCT02538536	Open-label, single arm; n = 40	Abnormal laboratory values and/or adverse events over 9 months	Completed January 2017
BG00011 (Biogen) (formerly STX-100)	Integrin αvβ6 monoclonal antibody	NCT01371305	Randomised, placebo-controlled, dose escalation; n = 40	Adverse events over 16 weeks	Completed March 2017
SAR156597 (Sanofi)	IL-4 and IL-13 bispecific monoclonal antibody	NCT01529853	Randomised, placebo-controlled; n = 24	Adverse events over 6 months	Completed October 2013
		NCT02345070	Randomised, placebo-controlled; n = 300	Change in FVC % predicted at week 52	August 2017
PRM-151 (Promedior, Inc. [Bristol-Myers Squibb])	Recombinant form of pentraxin-2 (PTX-2)	NCT02550873	Randomised, placebo-controlled; n = 117	Change in FVC % predicted at week 28	March 2017
KD025 (Kadmon Corporation, LLC)	Rho-associated kinase 2	NCT02688647	Randomised, open-label, active comparator; n = 36	Change in FVC at week 24; adverse events over 24 weeks	March 2017
GBT440 (Global Blood Therapeutics)	Haemoglobin modifier	NCT02846324	Randomised, placebo-controlled; n = 30	Adverse events over 28 days	April 2017
Tipelukast (MediciNova)	Non-selective inhibitor of PDE, 5-LO, LT, phospholipase C and thromboxane A2	NCT02503657	Randomised, placebo-controlled; n = 15	Change in FVC at week 26	June 2017
GLPG1690 (Galapagos NV)	Autotaxin inhibitor	NCT02738801	Randomised, placebo-controlled; n = 24	Safety and tolerability over 12 weeks; pharmacokinetics; concentration of lysophosphatidic acid in blood/BALF	June 2017
FG-3019 (FibroGen)	Connective tissue growth factor (CTGF) inhibitor	NCT01890265	Randomised, placebo-controlled; n = 136	Change in FVC % predicted at week 48	June 2017
		NCT01262001	Open-label, dose escalation; n = 89	Safety and tolerability (different time frames per cohort)	April 2018
Lebrikizumab (Hoffmann-La Roche)	IL-13 monoclonal antibody	NCT01872689	Randomised, placebo-controlled and active controlled; n = 484	Change in FVC % predicted at week 52	November 2017
CC-90001 (Celgene)	JNK inhibitor	NCT03142191	Randomised, placebo-controlled; n = 135	Change in FVC % predicted at week 24	May 2020

[a] According to www.ClinicalTrials.gov.

Phase II study in patients with IPF (N = 41), PBI-4050 800 mg once daily with or without nintedanib or pirfenidone for 12 weeks was well tolerated. PBI-4050 in combination with nintedanib significantly reduced change from baseline in FVC at week 12 versus PBI-4050 plus pirfenidone or PBI-4050 alone [61].

3.8. Tipelukast (MN-001)

Tipelukast (MN-001; MediciNova) is an orally administered, small molecule, non-selective phosphodiesterase (PDE), 5-lipoxygenase (5-LO), leukotriene, phospholipase C and thromboxane A2 inhibitor [62]. The anti-fibrotic effects of tipelukast are believed to be mediated via inhibition of 5-LO and the 5-LO/leukotriene pathway [62]. In mice with bleomycin-induced lung fibrosis, tipelukast reduced fibrosis (assessed histologically) and reduced the tissue density and hydoxyproline content of the lungs [62]. In lung biopsies from patients with IPF, the 5-LO metabolic pathway was observed to be constitutively activated, with strong correlations between tissue leukotriene levels and the degree of inflammation and fibrosis [63]. Investigation of tipelukast as a treatment for asthma has shown it to be safe and well tolerated [64]. No data on the efficacy or safety of tipelukast in patients with fibrotic lung disease has been presented.

3.9. BG00011

BG00011 (Biogen) is a subcutaneously administered humanised monoclonal antibody against αvβ6 integrin. αvβ6 integrin is a tissue-restricted activator of TGF-β that is upregulated in the lung tissue of patients with IPF compared with normal lung tissue [65]. Partial inhibition of TGF-β using a monoclonal antibody against αvβ6 integrin given in a preventive or therapeutic manner attenuated bleomycin-induced pulmonary fibrosis in mice [65]. No data on the efficacy or safety of BG00011 in humans has been presented.

3.10. PRM-151

PRM-151 (Promedior/Bristol-Myers Squibb) is an intravenously administered recombinant form of human pentraxin 2 [66]. Pentraxin 2, also known as serum amyloid P (SAP) or PTX2, is a plasma protein that is a potent inhibitor of fibrocyte differentiation from monocytes/macrophages [67]. In animals with bleomycin-induced fibrosis, administration of pentraxin 2 reduces collagen content and α-SMA levels [68,69].

Patients with IPF show reduced levels of pentraxin 2 [70]. In a randomised, double-blind, single ascending dose study in healthy volunteers (N = 26), single doses of PRM-151 up to 20 mg/kg were well tolerated, with no dose-limiting adverse events [66]. When a single dose of PRM-151 (10 mg/kg) was administered to 3 patients with IPF, elevated IL-6 levels were reduced, as were circulating fibrocytes [66]. In a Phase I randomised, double-blind, placebo-controlled ascending dose study in patients with IPF (N = 21), PRM-151 given on days 1, 3, 5, 8 and 15 was generally well tolerated [71]. The most common adverse events were cough, fatigue and headache, which were not dose dependent. FVC % predicted and 6-min walk distance showed trends towards improvement in patients treated with PRM-151 versus placebo [71], and plasma levels of surfactant protein D and VEGF tended to be lower [72].

3.11. KD025

KD025 (or SLX-2119; Kadmon Corporation, LLC) is an orally administered selective Rho-associated protein kinase 2 (ROCK2) inhibitor. Healing responses to tissue injury involve reorganisation of the actin cytoskeleton of participating cells, which is directed by the ROCK family of serine/threonine kinases, including ROCK1 and ROCK2 [73]. ROCK activation has been demonstrated in the lungs of patients with IPF and in mice with bleomycin-induced lung fibrosis [74]. Myofibroblasts isolated from the lungs of patients with IPF demonstrated high constitutive ROCK activity compared with those from normal lungs [74]. KD025 has anti-inflammatory effects in human T cells and dose-dependently attenuates lung fibrosis in a bleomycin-induced fibrosis model [75]. No data on the efficacy or safety of KD025 in humans has been presented.

3.12. Lebrikizumab

Lebrikizumab (Hoffmann-La Roche) is a subcutaneously administered monoclonal antibody targeting IL-13 [76]. IL-13 promotes the differentiation of monocytes into fibrocytes and regulates ECM generation; it is thus a potent mediator of lung fibrosis [67,77]. Increased expression of IL-13 and activation of IL-13 pathways are evident in the lungs of patients with IPF [77].

Lebrikizumab blocks IL-13 signalling by interfering with the binding of IL-13 to IL-4Rα of the heterodimeric combination of IL-13Rα1 and IL-4Rα receptors [76]. In a mouse model of pulmonary fibrosis, targeting IL-13 with a monoclonal antibody attenuated lung fibrosis and the accumulation of ECM [77]. Investigation of lebrikizumab as a treatment for moderate to severe asthma has shown it to be safe and well tolerated [78]. No data on the efficacy or safety of lebrikizumab in patients with fibrotic lung disease has been presented.

3.13. SAR156597

SAR156597 (Sanofi) is a subcutaneously administered monoclonal antibody targeting both IL-4 and IL-13 [79]. IL-4 induces TGF-β production by fibroblasts and is a chemotactic factor for the directed movement of pulmonary fibroblasts [80]. Elevated IL-4 levels have been found in the lungs of patients with IPF [81].

SAR156597 inhibits IL-4Rα, which binds IL-4, the heterodimeric combination of IL-13Rα1 and IL-4Rα, which binds IL-4 and IL-13 and IL-13Rα2, which binds IL-13 [79]. In cell-based assays, SAR156597 inhibited activities mediated by IL-4 and IL-13 and suppressed IL-4/IL-13-induced fibroblast activation [82]. No data on the efficacy and safety of SAR156597 in humans has been presented.

3.14. FG-3019

FG-3019 (FibroGen) is an intravenously administered monoclonal antibody targeting human *anti*-CTGF. CTGF (also known as CCN2) is a matricellular protein that mediates tissue remodelling and fibrosis, acting to promote fibroblast migration, the formation and activation of myofibroblasts, and ECM deposition [83,84]. CTGF is induced by TGF-β and studies in animal models suggest that the combination of TGF-β and CTGF is required to elicit overt tissue fibrosis [85]. FG-3019 has been shown to reduce lung fibrosis in a number of animal models [84,85]. CTGF is elevated in serum and lung tissue from patients with IPF [86,87].

Results at week 48 from a Phase II open-label study of FG-3019 (15 mg/kg i.v. or 30 mg/kg i.v. every 3 weeks) in 89 patients with IPF showed that both doses were generally well tolerated [88]. The mean absolute change in FVC % predicted at week 48 was −2.7± 0.8% (n = 66). At week 48, interstitial lung disease scores based on HRCT had improved or were stable in 35% of 67 patients, while 29% of 68 patients had no decline in FVC % predicted [88]. A randomised placebo-controlled Phase II clinical trial of FG-3019 in patients with IPF, with change in FVC % predicted as the primary endpoint, is underway.

3.15. GBT440

GBT440 (Global Blood Therapeutics) is an orally administered small molecule, which binds to the N-terminal α chain of haemoglobin, increasing its affinity for oxygen. It was originally developed for patients with sickle cell disease [89], but may be a beneficial therapeutic agent for the treatment of other diseases where oxygen saturation is low. Recruitment is underway for a 28-day trial of GBT440 in patients with IPF and oxygen desaturation after exercise to assess its tolerability and effects on oxygen saturation assessed using pulse oximetry.

3.16. CC-90001

CC-90001 (Celgene) is an orally administered c-Jun N-terminal kinase (JNK) inhibitor with bias for JNK1 over JNK2. In a preclinical model, CC-90001 attenuated lung collagen and α-smooth muscle actin [90]. In a Phase I study in healthy volunteers, CC-90001 dose-dependently reduced c-Jun phosphorylation induced by UV radiation [90]. Nausea was the most commonly reported AE (8–15% of patients depending on dose) over 12 weeks. A randomised placebo-controlled Phase II clinical trial of CC-90001 in patients with IPF, with change in FVC % predicted as the primary endpoint, is planned [NCT03142191].

4. Potential combination therapy

It is expected that using a combination of drugs might improve treatment efficacy and response rates in IPF compared to single therapies, as is the case with most cancers [7,91,92]. One of the major challenges ahead is the question of which compounds to combine and how to evaluate combination therapies in clinical trials. The drugs most likely to provide additive efficacy when used in combination with one of the approved therapies are those with alternative, complementary, or synergistic mechanisms of action. Drugs with overlapping adverse event profiles are less likely to make good combination partners. Clinical development of combination therapies will be challenging, as combination therapies will need to demonstrate superior efficacy to monotherapies that have already been shown to reduce disease progression in patients with IPF. This may require the use of different endpoints, or the enrolment of subgroups of patients with IPF, for example patients with

rapidly progressing disease, or disease that is refractory to monotherapy.

A new drug with putative direct activity on EMT, FMT, extracellular matrix deposition, resolution of fibrosis by fibroblast apoptosis, stimulation of re-epithelialisation, or oxidative stress might be a suitable combination partner for nintedanib to complement the potent mechanistic activities that have been demonstrated for nintedanib. This could be investigated in *in vitro* assays using human cellular systems resembling aspects of the pathogenic processes active in IPF and in animal models, although all such experiments have limitations with respect to how closely they model the processes that drive fibrosis in patients with IPF. Identifying a suitable combination partner for pirfenidone could be more challenging, as *in vitro* assays using human cells have only shown activity when the concentrations of pirfenidone used were far higher than those achieved in patients. This suggests that *in vivo* exploration in animal models of lung fibrosis may provide the best means of exploring the additive efficacy of therapies used in combination with pirfenidone.

5. Conclusions

Advances in our understanding of the pathogenesis of IPF have identified numerous targets for potential therapeutic intervention. Several potential therapies that have shown activity in pre-clinical models are currently under investigation in Phase II trials. The complexity of the pathogenic processes active in IPF means that ultimately combination therapy is likely to provide the most effective treatment. Mechanistic findings from *in vitro* and *in vivo* explorations are critical to provide guidance on the combinations that are most likely to be effective, but it is only through well-designed clinical trials that the efficacy and safety of combination therapies can be determined.

6. Conflict of interest statement of article on treatment targets in IPF

The authors have reported to Respiratory Medicine the following conflicts of interest:

MK reports receipt of grants and personal fees from Boehringer Ingelheim and Roche; personal fees from GlaxoSmithKline, Gilead, AstraZeneca, ProMetic and Genoa; and grants from Actelion, Respivert, the Canadian Institutes of Health Research (MOP-136950), and the Canadian Pulmonary Fibrosis Foundation. FB reports receipt of speakers honoraria and travel costs reimbursement from Boehringer Ingelheim, Roche and Serendex. LW is an employee of Boehringer Ingelheim.

Acknowledgments

Editorial assistance, supported financially by Boehringer Ingelheim, was provided by Clare Ryles and Wendy Morris of FleishmanHillard Fishburn, London, UK during the preparation of this article. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and have approved the final version.

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