The therapy of idiopathic pulmonary fibrosis: what is next?

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There is still no cure for IPF. Clinical trials focus on new therapeutic targets, improvements in nonpharmacological therapies and treatment of comorbidities and acute exacerbations. All future therapies should aim to reduce the burden of disease. http://bit.ly/2XdxqAP

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ABSTRACT Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing interstitial lung disease, characterised by progressive scarring of the lung and associated with a high burden of disease and early death. The pathophysiological understanding, clinical diagnostics and therapy of IPF have significantly evolved in recent years. While the recent introduction of the two antifibrotic drugs pirfenidone and nintedanib led to a significant reduction in lung function decline, there is still no cure for IPF; thus, new therapeutic approaches are needed. Currently, several clinical phase I–III trials are focusing on novel therapeutic targets. Furthermore, new approaches in nonpharmacological treatments in palliative care, pulmonary rehabilitation, lung transplantation, management of comorbidities and acute exacerbations aim to improve symptom control and quality of life. Here we summarise new therapeutic attempts and potential future approaches to treat this devastating disease.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, fibrosing idiopathic interstitial lung disease (ILD) characterised by progressive scarring of the lung parenchyma associated with a steady worsening of respiratory symptoms, and decline of pulmonary function, ultimately leading to death [1, 2].

Despite constant efforts, many therapeutic approaches failed until antifibrotic therapy fundamentally altered the therapeutic approach in IPF (figure 1). Currently, two antifibrotic therapies are available: pirfenidone and nintedanib. Pirfenidone has proven anti-inflammatory, antioxidant and antifibrotic effects. After an early feasibility study [4], prospective studies demonstrated that pirfenidone reduces the decline of forced vital capacity (FVC) in patients with IPF [5–8]. *Post hoc* analysis of the pivotal international phase III studies described a significant reduction of the risk in FVC decline, death, disease progression, 6-min walk distance (6MWD) and dyspnoea in the pirfenidone-treated patients compared to placebo [9]. Further *post hoc* analyses described a significant reduction in respiratory-related hospitalisation [10, 11], and consistent effects of pirfenidone in all subgroups analysed, *e.g.* with regards

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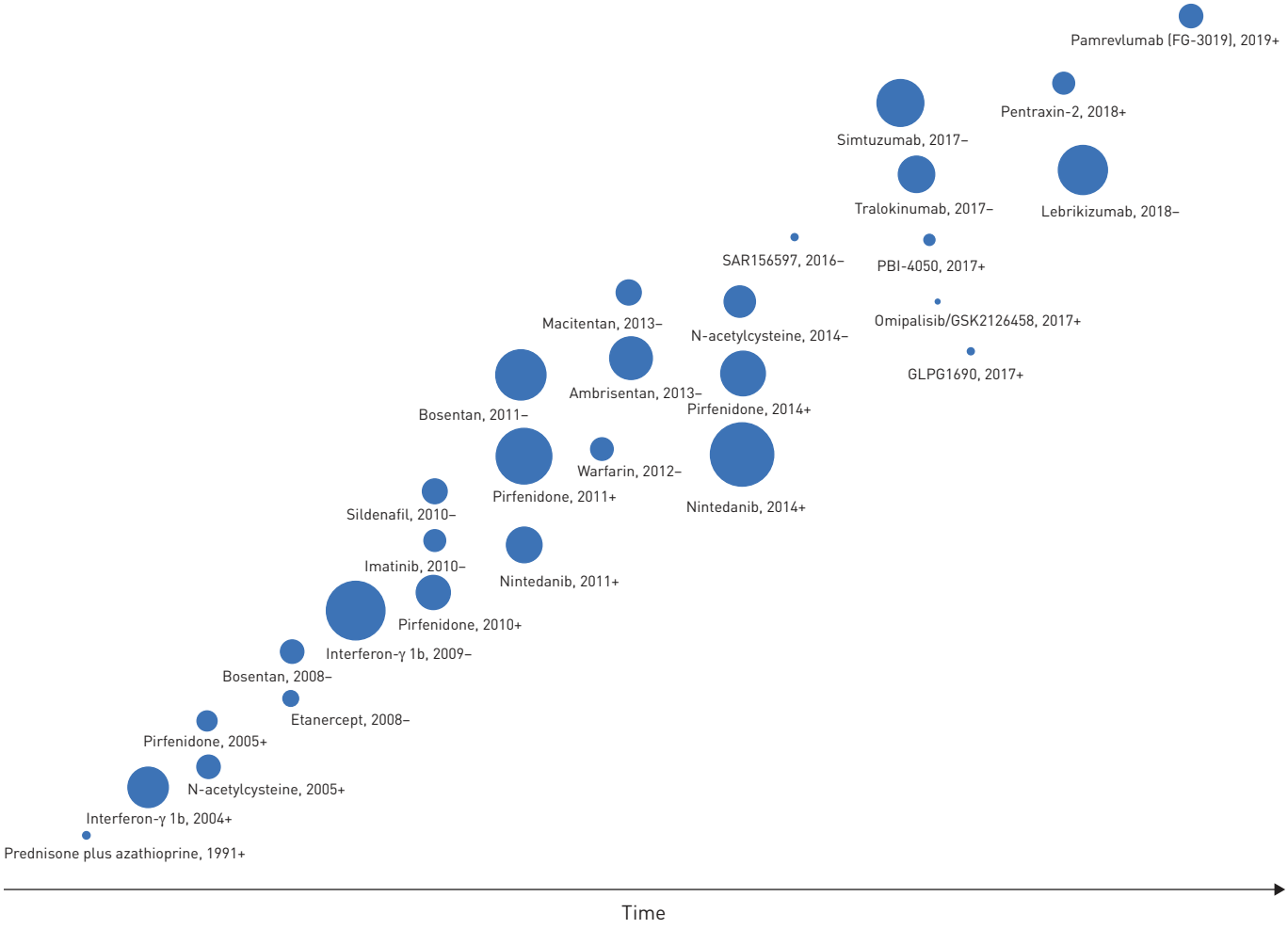

FIGURE 1 Evolution of treatment in idiopathic pulmonary fibrosis (IPF). Schematic representation of clinical trials of therapy performed for IPF in the past three decades. Circle sizes are an approximate representation of the sample sizes of the clinical trials. +: study ended with positive outcome; –: study ended with negative outcome. Reproduced and modified from [3] with permission.

to FVC decline, 6MWD, health-related quality of life (HRQL) [9, 12]. Furthermore, pirfenidone is associated with adequate safety and tolerability [13]. Nintedanib is a tyrosine kinase inhibitor where *in vitro* analyses have demonstrated inhibitory effects on fibroblast proliferation and differentiation [14, 15]. Phase II and III studies described significant effects on reducing lung functional decline. Additionally, the key secondary end-point, time to the first acute exacerbation, favoured the use of nintedanib [16, 17]. *Post hoc* analyses showed consistent effects of nintedanib reducing FVC decline regardless of the underlying radiological pattern, presence of emphysema or other important baseline characteristics [18, 19], and was effective in patients with more advanced disease [20]. Nintedanib has an adequate safety and tolerability profile [16, 17].

ABCDE and future approaches in IPF

To ensure an optimal patient based approach in IPF, management may be guided by an ABCDE algorithm: Assessment of the needs of patients and caregivers; Backing up the patient with educational resources, self-management strategies and pulmonary rehabilitation; Comfort-care (symptom-based therapies) and treatment of Comorbidities; Disease-modifying treatments; and End-of-life care [21]. Yet, despite significant progress in the treatment of IPF, there is still no cure, and thus new concepts in treatment are needed. These strategies may include therapeutic biomarkers guiding therapy, the use of combination therapies, novel drugs targeting new pathways in fibrosis, therapies aimed at targeting the lung microbiome, novel nonpharmacological therapies with developments in lung transplantation, new ways to approach palliative care, improved treatment of comorbidities and an important unmet need in treatment of acute exacerbation of IPF (AE-IPF).

Biomarkers guiding therapy

A prerequisite for future personalised therapy for IPF is the development of biomarkers that can guide diagnostic, therapeutic and prognostic approaches in managing IPF. Several potential peripheral blood, molecular and radiological biomarkers have been identified and are summarised in table 1.

Diagnostic biomarkers

Accurate diagnosis in IPF remains a challenge and the current gold standard of performing a lung biopsy according to guideline recommendations [1, 2] is not without significant risk [55], and thus often not possible. Thus, the identification of specific biomarkers that can facilitate the accurate diagnosis of IPF is of great interest. A number of peripheral blood biomarkers have been studied that can aid in delineating ILDs from other severe lung diseases. The markers Krebs von den Lungen (KL)-6 [24], chitinase-like protein (YKL40) [41, 56], leucocytes and circulating innate immune cells [57–59], surfactant proteins (SP)-A, -B, -D, among others, have been shown to discriminate IPF from healthy controls [25, 27, 31]. KL-6 may also discriminate ILDs from other benign lung diseases [24, 60]. Another valuable biomarker is the matrix metalloproteinase (MMP)7, where higher levels are related to interstitial lung abnormalities [33]. Furthermore, MMP7 and MMP1 may distinguish between IPF and hypersensitivity pneumonitis [32]. The PROFILE (Prospective Study of Fibrosis in Lung Endpoints) study, the first study to perform a sequential evaluation of >100 serum protein biomarkers, demonstrated that markers of epithelial injury and matrix degradation are important in IPF. The study showed that levels of epidermal growth factor receptor and clusterin were lower and levels of MMP1, MMP7 and SP-D were significantly elevated in IPF patients compared to healthy controls [25]. In addition, PROFILE revealed that oncostatin M and cytokeratin 19 fragment (CYFRA-21-1) were able to distinguish IPF patients from healthy controls [47]. The biomarkers KL-6 and SP-D have been used widely in the diagnostic pathways for IPF in Japan [61]. However, currently, the clinical utility of the abovementioned serum biomarkers is still limited and thus they are not recommended for diagnostic purposes in IPF [2].

Prognostic biomarkers

Progression in IPF is challenging to predict due to the heterogeneity of the population. FVC decline has been shown to be a predictor of mortality in IPF [62] and is the most robust measure adopted in clinical trials. However, baseline FVC does only have limited prognostic value and longitudinal changes in FVC have some weaknesses [63]. Therefore, composite scoring systems incorporating lung physiology, sex and age are deemed more accurate at predicting mortality [64, 65]. It is recognised that biomarkers may augment these models and improve prognostication in IPF. Several biomarkers have been studied that show significant association with prognosis in IPF (table 1) [22, 23, 26, 28–30, 34–40, 42–44]. High MMP7 has shown significant correlations with IPF disease severity as defined as lung function parameters (FVC and diffusion capacity of the lung for carbon monoxide (*D*LCO), and increased breakdown products of MMP activity predicted worse survival in IPF [33].

Furthermore, the PROFILE study showed that C reactive protein degraded by MMP1/8 (CRPM) discriminated IPF from healthy subjects and stable from progressive subjects, predicted progression and indicated poor overall survival [45]. Other predictors of progression and survival in IPF were SP-D and cancer antigen (CA)19-9, -125 [46].

The ongoing INMARK study will assess the effect of nintedanib, on the rates of change of biomarkers of extracellular matrix (ECM) turnover in patients with IPF, their ability as predictors of disease progression and whether the drug alters associations between changes in biomarkers and disease progression [66].

Radiological biomarkers

Several studies have been published in recent years on the potential of high-resolution computed tomography (HRCT) patterns as prospective prognostic biomarkers [67]. A recent study reported about the potential of quantitative computed tomography (CT) tools such as Data-Driven Textural Analysis (DTA) [68]. In this study, automated recognition of IPF on CT resulted in a severity index that correlated with visual and functional changes [68]. Yet, there is still a high need for elaboration of automated, visual CT scoring *via* machine learning development process and for creation of expanded datasets supporting this process [69]. The importance of functional respiratory imaging (FRI) providing quantitative visualisation of different patterns was recently highlighted, where FRI correlated with FVC decline [70]. Furthermore, CT densitometry, especially the area right of the inflexion point in HRCT histogram was reported to correlate with lung function decline [71]. Jacob *et al.* [72] reported recently that a computer scoring based quantification of parenchymal patterns including vessel-related structure scores predicted IPF mortality and functional decline in IPF. Hyperpolarised xenon-129 magnetic resonance imaging could be a potential non-invasive method for estimating gas-exchange impairment in IPF, as this inert gas is able

TABLE 1 Peripheral blood and molecular biomarkers in idiopathic pulmonary fibrosis (IPF)

	Mechanism of action	Outcome of the study	Effect on IPF
Circulating blood biomarkers			
CCL18	Alternative macrophage activation Upregulation of collagen production by lung fibroblasts	Higher mortality in patients with serum CCL18 concentrations >150 ng·mL^{-1}, higher incidence of disease progression in the group with high serum CCL18 concentrations [22]	Predicts progression and mortality in IPF
ICAM-1	Adhesion molecule Marker of oxidative stress in the lungs	Predicts poor overall, transplant-free and progression-free survival [23]	Predicts mortality in IPF
KL-6/MUC1	High molecular weight glycoprotein expressed at ECM surface of type II pneumocytes	Significantly higher level in ILDs [24] Higher levels among patients who died within the study period [25] Lower survival of patients with high KL-6 [26]	Discriminates ILDs from other benign lung diseases Predicts mortality in IPF
SP-A	Surfactant proteins produced by type II pneumocytes	High level in IPF [27] Independent predictor of survival [28] Associated with the time to death or lung transplantation [29] Predictive effect on those with UIP in HRCT [30]	Discriminate IPF from other ILDs SP-A, SP-D predict mortality in IPF
SP-B		Higher level in IPF [31]	
SP-D		High level in IPF [25] Independent predictor of survival time better related to parenchymal involvement [27]	
MMP1	Zinc-dependent proteases involved in the breakdown of ECM components	Distinguish between IPF and HP [32] Elevated levels in IPF [25]	Discriminates IPF from other ILDs
MMP7	MMP1 the most highly expressed interstitial collagenase degrading fibrillar collagens MMP7 the smallest member capable of degrading multiple components of ECM	Distinguish between IPF and HP [32] Elevated levels in IPF [25] Related to FVC decline, to higher prevalence of exertional dyspnoea, to ILAs on HRCT and to higher all-cause mortality [33]	Discriminates IPF from other ILDs Predicts mortality in IPF
BNP	Natriuretic peptide secreted by cardiac ventricles	Correlation with clinical status, functional exercise testing parameters, functional WHO class II, III [34]	Relates to haemodynamic parameters and prognostic value in patients with left or right heart failure
VEGF	Growth factor regulating angiogenesis enhancing vascular permeability	Positive correlation with HRCT interstitial score, influence on monthly FVC decline [35]	Reflects severity and predicts progression of IPF
CD28 downregulation on CD4$^+$ T52 cells	CD28 co-stimulatory molecule providing signal for activation of naive CD4 lymphocytes	Correlated with decreased FVC and freedom from major adverse events (death or lung transplantation) [36]	Predicts progression, mortality in IPF
HSP70 IgG antibodies	HSP70 antibody working against HSP70 autoantigene and activating IL-8 production of monocytes	Associated with decreased FVC and 1-year survival [37]	Predicts progression, mortality in IPF
Periostin	Fibroblast activating matrix proteins	Negative correlation with monthly changes in VC, D_{LCO} [38] Increase of honeycombing score on HRCT, predictor of shortened overall survival, time-to-event [39]	Predicts progression, mortality in IPF
Osteopontin	Glycoprotein secreted by osteoclasts, macrophages and activated T-cells	Reverse correlation with arterial oxygen tension [40]	Predicts progression in IPF
YKL40	Chitinase-like protein	Elevated levels in ILDs, correlated with poor survival [24, 41]	Discriminates ILDs from healthy subjects Predicts mortality in IPF, remains predictive after 3–4 years
BLys	Plasma B lymphocytes stimulating factor	Correlated with pulmonary artery pressures, subjects with higher BLys diminished 1-year survival compared to those with lower BLys [42]	Predicts PH and survival in IPF

Continued

TABLE 1 Continued

	Mechanism of action	Outcome of the study	Effect on IPF
Circulating fibrocytes	Produce ECM components, mesenchymal markers Potential role in myofibroblast differentiation	High levels correlated with poor survival regardless to preservation of lung function, counts increased further during AE-IPF [43]	Predicts survival in IPF
CXCL13	Chemokine playing a role in autoimmune processes, mediating B-cell homing to inflammatory foci	High levels correlated with poor FVC and poor major event-free survival (*i.e.* transplant-free survival) [44]	Predicts progression, mortality in IPF
EGFR	Epidermal growth factor required for TGF-β1-induced epithelial-mesenchymal transition Crucial in signalling in bronchial epithelium	Lower levels in IPF [25]	Discriminates IPF from healthy subjects
Clusterin	Known as apolipoprotein J Glycoprotein upregulated by cytotoxic stimuli, maintaining epithelium viability during lung repair	Lower levels in IPF [25]	Discriminates IPF from healthy subjects
CRPM	C reactive, acute-phase protein degrading by matrix metalloprotease	Higher levels in IPF, could discriminate between stable and progressive subjects and indicated poor overall survival [45]	Discriminates IPF from healthy subjects Predicts progression, mortality in IPF
CA-19-9	Tumor markers, mucous associated carbohydrate antigens increasing in metaplastic epithelium in fibrotic lesions Associated with mucous secretion within honeycomb cysts	High levels highly predictive of progressive fibrosis [46]	Predicts progression, mortality in IPF
CA-125		Rising levels predicted both disease progression and overall survival [46]	
OSM	Glycosylated protein, member of IL-6 family of ligands	Identified baseline prognosis and longitudinal change in individuals with IPF [47]	Discriminates ILDs from healthy subjects Predicts progression, mortality in IPF
CYFRA-21-1	Intermediate filaments in the cytoskeleton of alveolar and bronchiolar epithelial cells Marker of epithelial cell damage	Identified baseline prognosis and longitudinal change in individuals with IPF [47]	Discriminates ILDs from healthy subjects Predicts progression, mortality in IPF
Molecular biomarkers			
MUC5B	Mucin associated with the development of both familial interstitial pneumonia and sporadic IPF	MUC5B promoter gene polymorphism associated with improved survival independent of clinical factors [48]	Predicts survival in IPF
uPAR	Plasminogen activator receptor augmenting monocyte adhesion	Elevated serum levels through macrophage overexpression in IPF compared to controls [49]	Discriminates IPF from healthy subjects
TERT	Reverse transcriptase maintaining telomere integrity	Mutation associated with familial interstitial pneumonias [50] and sporadic, adult-onset IPF [51]	Discriminates familial ILDs and IPF from healthy subjects
Telomere length	Length of nucleoprotein structures that protect chromosomal ends	Shorter telomere length associated with progression-free survival of IPF [52]	Predicts survival in IPF
TLR3	Receptor mediating innate immune response to tissue injury, inflammation and viral infection	Polymorphism associated with early lung function decline and death [53]	Predicts progression, mortality in IPF
α-Defensin	Antimicrobial peptides presenting in granules of neutrophils inhibiting activation of the classical complement pathway	Increased α-defensins localised in the epithelium of the lungs and apoptosis of epithelium in AE-IPF [54]	Predicts AE-IPF

CCL18: CC chemokine ligand 18; ICAM-1: intercellular adhesion molecule 1; KL: Krebs von den Lungen; MUC: mucin; SP: surfactant protein; MMP: matrix metallopeptidase; BNP: brain natriuretic peptide; VEGF: vascular endothelial growth factor; HSP: heat shock protein; Ig: immunoglobulin; YKL40: chitinase-like protein; BLys: plasma B lymphocytes stimulating factor; CXCL: C-X-C motif chemokine ligand; EGFR: epidermal growth factor receptor; CRPM: C-reactive protein degraded by metalloproteinase-1/8; CA: cancer antigen; OSM: oncostatin M; CYFRA-21-1: cytokeratin 19 fragment; uPAR: urokinase-type plasminogen activator receptor; TERT: telomerase reverse transcriptase; TLR: toll-like receptor; ECM: extracellular matrix; ILD: interstitial lung disease; UIP: usual interstitial pneumonia; HRCT: high-resolution computed tomography; IL: interleukin; HP: hypersensitivity pneumonitis; FVC: forced vital capacity; ILA: interstitial lung abnormality; WHO: World Health Organization; VC: vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; PH: pulmonary hypertension; AE-IPF: acute exacerbation of idiopathic pulmonary fibrosis; TGF: transforming growth factor.

to image the distribution in airspaces as well as in the red blood cells of the vessels and in tissue of interstitial parenchyma [73].

Molecular biomarkers and genetic alterations in IPF

Several genomic biomarkers have been identified that can be predictive of the likelihood of developing IPF and thus may be helpful for diagnostic purposes [49, 54, 74, 75]. The mucin 5B promoter polymorphism (MUC5B) is a strong risk factor for developing sporadic and familial interstitial pneumonias with odds ratios as high as 21.8 (95% CI 5.1–93.5) for developing IPF in those homozygous for the T allele [48]. However, this polymorphism can be present in the normal healthy population at a significant frequency and thus is not specific for the development of IPF. Telomerase reverse transcriptase (TER-C/-T) gene mutations have been reported in familial interstitial pneumonias [50] and in sporadic, adult-onset IPF [51]. Besides TER mutations, short telomere length is also associated with outcome [52]. Toll-like receptor 3 polymorphism, a receptor mediating innate immune response to tissue injury, inflammation and infection showed associations with lung function decline and death [53]. Oldham *et al.* [76] have genotyped single nucleotide polymorphisms between toll-interacting protein (TOLLIP) and MUC5B genes that are associated with IPF susceptibility and survival, and assessed whether the polymorphisms of these genes could interfere with IPF therapies. In their *post hoc* study, the first significant drug–gene interaction in individuals with IPF was reported, as the TOLLIP rs3750920 TT genotype was associated with a response to N-acetylcysteine. Two studies demonstrated, that immune cell transcriptional profiles may change the response to the lung microbiome [58, 59] and showed association between genomic changes and changes in FVC, mortality and response to antifibrotic therapy [57]. However, personalised medicine is not yet established in IPF with regards to genetic alterations.

Therapeutic biomarkers

In a recent study, biomarkers were tested to interact with pirfenidone treatment and whether it could serve as prognostic, predictive or pharmacodynamic biomarker. There, pirfenidone treatment effects were consistent regardless of baseline biomarker levels, and pirfenidone treatment had no meaningful pharmacodynamic effect on the plasma levels of the prespecified biomarkers [77, 78]. In contrast, a Japanese retrospective analysis has shown prognostic effects of SP-D in an IPF cohort receiving pirfenidone [79]. Taken together, reliable predictive therapeutic biomarkers are still missing and the search for informative biomarkers in IPF must be continued [78].

New approaches in drug treatment in IPF

After several disappointing years of clinical trials of therapies that did not demonstrate efficacy in IPF (figure 1), the anti-fibrotic drugs pirfenidone and nintedanib have been associated with significant slowing of respiratory deterioration in IPF and perhaps prolonged survival [8, 17]. However, the response to antifibrotic treatment is heterogenous and may be limited by side-effects, necessitating the constant need to establish novel therapeutic approaches, including combination therapies and the development of novel compounds.

Combination therapies

The pathogenesis of IPF is a complex interplay of genetic and environmental factors activating numerous profibrotic pathways in multiple cell types [80]. Thus, it is hypothesised that targeting multiple pathways with current established therapies may show synergistic efficacy in IPF, whilst the combined adverse effects are of concern. The INJOURNEY trial [81] addressed this concern in its primary end-point investigating the safety and tolerability of combination therapy of nintedanib with add-on pirfenidone *versus* nintedanib alone in 105 IPF patients, over a 12-week period. The total number of adverse effects were similar in the two groups; however, nausea and vomiting occurred with greater frequency in the combination group. Despite this, adherence rates were similar in both groups, thus concluding that nintedanib plus pirfenidone therapy had a feasible safety and tolerability profile in IPF. While data have to be interpreted with caution, as the study was not appropriately powered to assess efficacy, there were promising exploratory effects on lung function decline in the combination therapy compared to nintedanib alone (12-week FVC decline of −13.3 mL *versus* −40.9 mL, respectively) [81]. In a further study, the safety of nintedanib added to pre-existing pirfenidone treatment in 89 IPF patients showed no new safety signals to the known safety profile of either therapy alone [82]. Previous concerns regarding drug–drug interactions between pirfenidone and nintedanib affecting pharmacokinetics and bioavailability [5] have been refuted [83]. While these data are promising with regards to tolerance and safety, an important next step would be to perform larger controlled studies to investigate the efficacy of these combination therapies. Other combination therapies in IPF have been less promising, with a phase II trial investigated the tolerability and safety of pirfenidone with add-on acetylcysteine, based on its antioxidative effects, yielding negative results [84].

Pulmonary hypertension frequently complicates severe fibrosis and is associated with diminished survival in IPF patients [84, 85]. Multiple clinical trials of monotherapies with PAH drugs targeting either pulmonary hypertension–IPF or IPF have yielded negative results [84–88]. However, a subgroup analysis of the STEP-IPF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis) trial of sildenafil, a phosphodiesterase-5 inhibitor, reported some positive secondary outcomes including improvements in oxygenation, D_{LCO} and, especially, HRQL [86]. These findings led to a combination study of nintedanib and sildenafil *versus* nintedanib alone, the INSTAGE study, in a severe cohort of IPF with D_{LCO} <35% predicted [87]. Unfortunately, the study failed to meet its primary end-point of HRQL at 12 weeks. Yet, some exploratory outcomes reported greater differences in HRQL, FVC decline and death at 24 weeks between the two groups. However, these observations are not statistically robust and need to be taken with caution. Subgroup analyses are still pending. An ongoing phase IIb trial (NCT02951429) currently examines the effect of combined sildenafil and pirfenidone therapy in patients with advanced IPF and risk of pulmonary hypertension [88].

Novel therapies

Our understanding of the complex pathogenesis of IPF continues to grow [80]. The repetitive alveolar epithelial cell injury is increasingly recognised as a crucial mediator of the fibrotic process with a complex interplay between host and environment. The activation of multiple pathways leading to fibroblast migration, proliferation and myofibroblast differentiation has identified numerous potential molecular targets of novel therapeutic agents currently being explored in early clinical trials. Here we summarise the key studies exploring these novel therapies in IPF (table 2).

Trials with positive outcomes

PRM-151 (pentraxin-2 analogues)

Pentraxin (PTX)-2, also known as serum amyloid P, is a circulating protein that binds to monocytes and inhibits the differentiation of monocytes into pro-fibrotic fibrocytes and transforming growth factor (TGF)-β producing macrophages, thus promoting epithelial healing and resolution of fibrosis [89–91]. Low PTX-2 levels have been observed in patients with IPF [92] and a recombinant human PTX-2 analogue (PRM-151) has been shown to ameliorate fibrosis in a bleomycin- and TGF-β-overexpressing animal model of fibrosis [93]. A phase I trial (NCT01254409) assessing safety and pharmacokinetics of PRM-151 in patients with IPF has shown a nonsignificant, but improving effect on FVC and 6MWD during the treatment period [94]. A further phase II study demonstrated significant effects in reducing pulmonary function decline and stability in 6MWD over 24 weeks compared to placebo with an acceptable safety profile [95]. The launch of a phase III trial for PRM-151 in IPF has been announced, using FVC as a primary end-point and 6MWD as a key secondary end-point.

Anti-connective tissue growth factor antibodies

Connective tissue growth factor (CTGF or CCN2) is normally expressed in low levels in healthy individuals. However, when expressed in excess it leads to upregulation of TGF-β, deposition of extracellular matrix (ECM) and inhibition of ECM degradation through the inhibition of metalloproteinases [96]. All these actions of CTGF are major profibrotic factors in the development of IPF. Elevated CTGF levels are measured in the bronchoalveolar lavage (BAL) of IPF patients [97, 98]. In the PRAISE study (NCT01890265), the CTGF antagonist pamrevlumab (FG-3019) was determined to have a significant effect on the reduction of the lung function decline of 160 IPF patients, yet full peer-reviewed data are still awaited [99]. The initiation of phase III trials has currently been announced.

PBI-4050

PBI-4050 is an analogue of a medium-chain fatty acid showing affinity towards G-protein receptors targeting and inhibiting multiple pathways involved in pulmonary fibrosis including inhibition of endoplasmic reticulum stress and reactive oxygen species production, epithelial–mesenchymal transition and fibrocyte/fibroblast recruitment, migration, proliferation and differentiation [100]. A phase II trial of 40 IPF patients treated with PBI-4050 alone or in combination with antifibrotic drugs showed no safety concerns [101]. While there was slowing or stability in FVC over a 12-week treatment period with PBI-4050 alone and in the combination with nintedanib, a statistically significant greater decline in FVC was observed for the combination of PBI-4050 and pirfenidone. This was due to reductions in pharmacokinetic levels of PBI-4050 in combination with pirfenidone, suggesting a possible drug–drug interaction. Additional studies of PBI-4050 alone or in combination with nintedanib are currently being planned.

TABLE 2 Current phase II–III trials in idiopathic pulmonary fibrosis (IPF)

	Mechanism of action	Clinical trial identifier	Study description	Primary outcome measures	Phase of development	Treatment duration
PRM-151	Recombinant form of human SAP	NCT02550873	Randomised, double-blind, placebo controlled	Change from baseline in FVC % pred	II	28 weeks
Simtuzumab	Anti-LOX antibody	NCT01769196	Randomised, double-blind, placebo-controlled	The effect of simtuzumab (GS-6624) on progression-free survival	II	148 weeks
Tipelukast	Leukotriene antagonists	NCT02503657	Randomised, double-blind, placebo controlled	Change from baseline FVC at 26 weeks	II	26 weeks
Tralokinumab	Anti IL-13 antibody	NCT01629667	Randomised dose-ranging	Change from baseline FVC % pred at week 52	II	52 weeks
SAR156597	Anti IL-4 and IL-13 antibody	NCT01529853	Randomised, double-blind, placebo-controlled	Safety/tolerability: number of participants with adverse events	II	6 weeks
Lebrikizumab	Anti IL-13 antibody	NCT01872689	Randomised, double-blind, placebo-controlled	Annualised rate of decrease in FVC % pred over 52 weeks	II	52 weeks
BG00011	Anti-integrin antibody	NCT03573505	Randomised, double-blind, placebo-controlled	Yearly rate of change in FVC	II	52 weeks
Pamrevlumab (FG-3019)	Anti-CTGF antibody	NCT01890265	Randomised, double-blind, placebo-controlled	Change from baseline in FVC % pred at week 48	II	48 weeks
PBI-4050	GPR84 antagonist/ GPR40 agonist	NCT02538536	Open-label, single arm, exploratory, observational study	Number of subjects with abnormal laboratory values and/or adverse events that are related to treatment	II	20 weeks
KD025	Selective inhibitor of ROCK2	NCT02688647	Randomised, phase 2, open-label	Change in FVC in baseline to 24 weeks	II	24 weeks
CC-90001	Kinase inhibitor targeting JNKs	NCT03142191	Randomised, double-blind, placebo-controlled	Percentage point change in FVC % pred	II	24 weeks
GLPG1690	Autotaxin-LPA inhibitor	NCT02738801	Randomised, double-blind, parallel group, placebo-controlled	Safety, tolerability, pharmacokinetic and pharmacodynamic properties of GLPG1690	II	12 weeks
Omipalisib/ GSK2126458	Inhibitor of PI3K/Akt pathway	NCT01725139	Randomised, double-blind, placebo-controlled	To explore a number of doses of GSK2126458 for engagement of pharmacology after short-term dosing	I	7–10 days
Sirolimus	mTOR inhibitor	NCT01462006	Double-blind placebo-controlled pilot study	Change in peripheral blood concentration of $CXCR4^+$ fibrocytes; number of subjects with drug side-effects	NA	22 weeks
Rituximab	Antibody targeting CD20	NCT01969409	Randomised, double-blind, placebo-controlled	Titres of anti-HEp-2 autoantibodies, by indirect immunofluorescence assays over 9 months	II	36 weeks
Co-trimoxazole or doxycycline	Antimicrobial drugs	NCT02759120	Randomised, un-blinded, phase III	Time to first non-elective, respiratory hospitalisation or all-cause mortality	III	9 months

SAP: serum amyloid P; FVC: forced vital capacity; LOX: lysyl oxidase; IL: interleukin; CTGF: connective tissue growth factor; GPR: G protein-coupled receptor; ROCK: ρ-associated coiled-coil containing protein kinase; JNK: Jun N-terminal kinase; LPA: lysophosphatidic acid; PI3K/Akt: phosphoinositide 3-kinase/protein kinase B. mTOR: mammalian target of rapamycin; CXCR: C-X-C chemokine receptor; HEp: human epithelial cell.

Autotaxin-LPA inhibitors

Autotaxin enzymes play a pivotal role in epithelial cell apoptosis and endothelial cell damage through the release of bioactive lysophosphatidic acid (LPA) [102]. Levels of LPA and autotaxin are increased in the BAL and exhaled breath condensates of IPF patients [103–105], and thus suggest the role of the autotaxin pathway in fibrosis. In a phase IIa study (NCT02738801, FLORA trial) the safety, tolerability, pharmacokinetic and pharmacodynamic profile of GLPG1690, a selective autotaxin and LPA inhibitor was analysed over a 12-week period. GLPG1690 was well tolerated by IPF patients with a similar safety profile, as placebo and preliminary efficacy analyses demonstrated encouraging results towards halting FVC decline [106]. Currently, international phase III trials to assess the efficacy of GLPG1690 in IPF are underway [107].

Trials with negative outcomes

Anti-lysyl oxidase antibodies

Lysyl oxidase-like 2 (LOXL2) plays an essential role in the cross-linking of collagen and elastin in the production of ECM [108] and elevated levels of LOXL2 are found in IPF [109]. A monoclonal antibody against LOXL2, simtuzumab, was examined in a recent study, where treatment was not associated with beneficial effects on progression-free survival in IPF [110].

Anti-interleukin antibodies

Interleukin (IL)-13 is a T-helper type 2 cell cytokine that has been implicated in promoting lung fibrosis in experimental models [111, 112]. Both IL-13 and IL-4 have an important role in the epithelial–fibroblast cross-talk. A number of monoclonal antibodies targeting IL-13 (the human IgG4 tralokinumab, SAR156597, an inhibitor of both IL-13 and IL-4, and lebrikizumab) have failed to show efficacy in IPF [113].

Ongoing trials

Leukotriene antagonists

Leukotrienes, due to their increased levels in IPF, may be used as therapeutic targets in the future [114, 115]. The leukotriene B4 antagonist tipelukast is currently explored in a phase II trial (NCT02503657) designed for efficacy, safety and tolerability end-points in moderate to severe IPF.

Protein kinase inhibitors

Protein kinases belong to the family of phosphorylation enzymes and inhibitors of protein kinases aim to block the action of these kinases. Several protein kinase inhibitors have been tested in IPF already, as acquired apoptosis resistance of myofibroblasts has been shown to be influenced by protein kinases [116]. A recent phase I study showed an appropriate tolerability of a selective protein kinase inhibitor of the Rho-associated coiled-coil containing protein kinase (ROCK)2. The trial is currently in its second phase II (NCT02688647), analysing further possibilities of ROCK2 [117]. A current phase II (NCT03142191) trial is evaluating CC-90001, a second-generation Jun N-terminal kinase (JNK) inhibitor for efficacy and safety after a first-generation JNK inhibitor (CC-930) showed effects on biomarker plasma levels [118].

Anti-integrin antibodies

Integrins as transmembrane receptors play a pivotal role in ECM adhesion, and integrin αvβ6 is involved in different fibrosing processes in the lungs. Based on this function, it may serve as a potential prognostic biomarker in ILDs [119]. A partial inhibition of integrin αvβ6 in rodents blocked the development of pulmonary fibrosing processes without aggravating inflammatory processes [120]. The safety and tolerability of a humanised monoclonal antibody (BG00011) against this integrin has been analysed in a phase II trial (NCT01371305). The study has been completed recently, data are still awaited.

PI3K/Akt pathway inhibitors

The phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) is a main signalling pathway for cell proliferation, differentiation, adhesion and survival [121, 122]. The inhibition of these isoforms may be associated with halting fibrosing processes [123, 124]. This idea was supported by a phase I study (NCT01725139) of omipalisib, a strong inhibitor of the PI3K/Akt pathway (GSK2126458), a potential PI3K/mammalian target of rapamycin (mTOR) inhibitor [125]. In a recently published study, omipalisib showed an acceptable tolerability profile in an IPF cohort [126]. In another phase II trial (NCT01462006), sirolimus, a drug targeting mTOR is currently under examination as a possible inhibitor of fibrotic activation in IPF.

CD-20 B-lymphocyte targeting drugs

B cell abnormalities such as plasma B lymphocytes stimulating factors (BLys) are present in sera, BAL and pulmonary parenchyma of IPF patients [37, 127, 128]. The CD20 surface molecule of B lymphocytes

could potentially be targeted by rituximab [42, 129]. Rituximab is currently being assessed in a phase II study of IPF (NCT01969409); however, results are pending. Furthermore, a phase II trial investigated rituximab *versus* combined plasma exchange, and standard of care with corticosteroids as a potential treatment option in AE-IPF was performed. While peer-reviewed results are pending, an interim report stated that 14.3% of the patients showed respiratory and 42.9% haemodynamic deterioration under combined plasma exchange, rituximab and corticosteroid therapy. 42.9% of patients survived to 60 days or to transplantation and 10% showed serious adverse events, and 40% showed non-serious adverse events (NCT01266317) [130].

Targeting the microbiome

Several lines of evidence imply that in IPF progression, acute respiratory deterioration including AE-IPF and mortality are associated with altered microbiome with increased bacterial load or abundance of possibly pathogenic microorganisms [59, 131]. Recent data suggest that lung dysbiosis is associated with inflammation and aberrant lung repair [131]. Thus, targeting the microbiome, *e.g.* by antibiotic drugs might be a possible therapy to slow progression of the disease. Co-trimoxazole, mainly thought of as an antibiotic, but perhaps also associated with immunomodulatory effects, has been studied previously in a randomised trial in IPF. While in the intention-to-treat analysis, no treatment effects were evident, in a per-protocol analysis, improvements in HRQL and reduction in mortality in IPF patients who remained on antibiotic therapy were seen [132]. The impact of co-trimoxazole or doxycycline on the time to first non-elective respiratory hospitalisation and/or on all-cause mortality is being analysed in a phase III study (NCT02759120) [133].

Developments in lung transplantation

Our understanding of the pathogenesis of IPF has improved significantly in recent years and new therapeutic options are emerging in this area; however, the disease is still considered to be incurable. Lung transplantation is a viable treatment option in IPF patients who continue to decline despite current licenced therapies. However, due to the relative contraindications to transplantation, such as the presence of multiple comorbidities in an ageing population that is IPF, lung transplantation may only be appropriate for a minority of patients with IPF [134]. Previously, the International Society for Heart and Lung Transplantation recommended lung transplantation for patients aged <65 years, but the changes made in 2014 have increased this to 70 years at least in some centres [135]. In this context, the United Network for Organ Sharing registry reported comparable post-transplant outcomes in patients aged >70 years to those aged 60–69 years [136]. Therefore, age has to be viewed in the context of the overall condition of the patient. Taking into account the dreadful outcomes, *e.g.* of AE-IPF, an early referral of patients with IPF for lung transplant evaluation is mandatory in those patients that are eligible for it [137].

The challenges attributed to meeting supply with demand and having sufficient organ donation vary from country to country, thus limiting lung donor availability, and unfortunately, in some countries many IPF patients still die waiting on the lung transplant list [138–140]. Accordingly, the appropriate triage of IPF patients according to disease severity and setting-up priorities within the waiting list are of particular importance. In 2005 the United States introduced the lung allocation score (LAS), a scoring system that prioritises lung transplantation according to severity of disease and estimated post-transplant survival. This system has also been adopted by all European transplant countries. The performance of the LAS has increased the number of lung transplantation performed in patients with IPF leading to IPF becoming the most common indication for lung transplantation in the US, and therefore leading to the reduction of waiting list time [141, 142]. Advances in lung transplantation technologies can impact on transplant survival. Nowadays, single, bilateral lobar and heart–lung transplantation is available in IPF [143]. There is little evidence separating single *versus* bilateral lung transplantation, although the number of bilateral transplants is increasing (single 39% *versus* bilateral 61%) [143]. Both methods have their advantages and disadvantages. Bilateral lung transplantation has shown increased long-term survival (65.2 months, interquartile range (IQR) 21.4–91.3 months *versus* single 50.4 months, IQR 17.0–87.5 months) [144] and less chronic lung allograft dysfunction, while single lung transplantation is a quicker and simpler method offering less cardiac manipulation and better peri-operative outcomes [143]. In a younger age group with lower LAS score, bilateral lung transplantation appears advantageous [145]. However, other factors can influence post-transplant survival. Pre-transplant IPF disease severity, use of extracorporeal membrane oxygenation (ECMO) and the presence of pulmonary hypertension or depression, as well as poorer quality of life and higher physiological distress 6 months post-transplant can result in poorer post-transplant survival [146, 147]. ECMO can be indicated in suitably robust IPF patients with severe respiratory failure who deteriorate rapidly despite maximal medical therapy [148]. A recent study demonstrated that patients undergoing ambulatory pre-transplant ECMO therapy had better post-transplantation outcomes than those undergoing lung transplantation from mechanical ventilation [149, 150].

Open questions remain regarding the continuation of antifibrotic therapy prior to lung transplantation. Data from small cohort studies suggest that antifibrotic drugs can be safely continued until lung transplantation [151, 152] and pirfenidone and nintedanib may also decrease the waiting-list mortality due to their disease progression attenuating effects [153]. Genetic markers such as shorter telomere length can also impact the post-transplantation prognosis by increasing the risk of post-transplant infections such as viral cytomegalovirus and thereby increasing the risks of allograft rejection. Genetic phenotyping of transplanted patients is therefore of importance.

Pulmonary rehabilitation

For years, pulmonary rehabilitation has been considered to have limited effect on patients with severe, chronic lung diseases such as IPF [1, 154], primarily due to the low number of articles on rehabilitation, small patient numbers and the lack of standardisation of the length and intensity of pulmonary rehabilitation programmes, making comparisons difficult. Following extensive growing research in this area, pulmonary rehabilitation is now recognised as an integral and essential component of management of patients with IPF and thus is a major feature of recommendations in national and international guidelines [2, 155]. A systematic Cochrane review exploring the impact of pulmonary rehabilitation in IPF reported that improvements of HRQL could be seen almost immediately after starting pulmonary rehabilitation while no adverse events have been reported [141]. However, no clear conclusions can be drawn in severe ILD and data on long-term effects of pulmonary rehabilitation in this advanced cohort are still sparse [156]. Current evidence on pulmonary rehabilitation in IPF shows significant short-term effects on improving exercise capacity (6MWD) and HRQL, while long-term effects are not maintained [157]. In addition, pulmonary rehabilitation has been shown to be useful in patients referred to lung transplantation [158]. Pulmonary rehabilitation should also include nutritional support [1], non-exercise components such as education [159], psychological [160] and symptom management [161], which are all of great importance in IPF.

Ongoing clinical trials are focusing on the outcomes of pulmonary rehabilitation in IPF. A study tested the 6MWD as the primary outcome and quality-of-life changes as secondary outcomes between active and inactive patient groups after a 12-week pulmonary rehabilitation programme (NCT03542318). The active group presented significantly better functional and health status after pulmonary rehabilitation [162]. Another ongoing study is testing the same outcomes comparing nintedanib *versus* nintedanib plus pulmonary rehabilitation patient groups (NCT03717012). A further ongoing trial aimed to determine the short- and long-term effects of oxygen supplementation during pulmonary rehabilitation in IPF (NCT03326089).

New ways to approach palliative intervention

Palliative interventions encompass a broad therapeutic spectrum including education and support of patients and caregivers, early management of symptoms with the goal of improving or maintaining quality of life of patients and end-of-life planning, in a disease which is invariably progressive and life-limiting [21]. Symptoms such as cough, breathlessness, anxiety and depression are common in IPF [163] and have a major impact on the quality of life of patients [164]. It has been proven that lower daily physical activity is associated with worse survival rates [165]. Palliative and supportive interventions in IPF with nonpharmacological and pharmacological interventions aim to improve these major symptoms, and are discussed briefly here.

Breathlessness can be an emotionally frightening and disabling symptom affecting mobility and quality of life and a breathing, thinking and functioning clinical model has been proposed to tackle this symptom [166]. Pulmonary rehabilitation is just one of many interventions that has been used to improve breathlessness. A multicentre prospective study of pulmonary rehabilitation has demonstrated improvements in the St George's respiratory questionnaire, 6-min walk test and breathlessness scores (Medical Research Council and Borg) [167]. Theoretically, oxygen therapy may be useful in improving dyspnoea at rest and during exertion and improving HRQL in IPF; however, studies demonstrating this benefit are limited.

International guidelines recommend the use of long-term oxygen therapy (LTOT) in IPF [1] with low-quality evidence. Oxygen therapy can increase self-confidence and active participation in various daily activities [168]; however, some limitations are described in daily life [169] and patients may develop a fear of being without oxygen after a longer period on LTOT [168]. Currently, there is no evidence of oxygen therapy impacting survival of ILD patients [170]. Conversely, ambulatory oxygen therapy (AmbOx) has been shown to be associated with improvements in HRQL in hypoxic ILD patients [171] and prolonged endurance time at ergometry. However, there was no impact on dyspnoea [172]. Its effect on exercise capacity varies in different studies [170, 172]. Therefore, AmbOx may represent an effective therapeutic option in this disease group.

The evidence for pharmacological therapies such as opiates and benzodiazepines for breathlessness management in IPF is scarce. A recent study reported that low-dose diamorphine reduced breathlessness without causing a fall in oxygen saturation in an elderly cohort with end-stage IPF [173]. As oral morphine therapy reduced dyspnoea and did not cause respiratory depression, low-dose opioids may be effective and safe in the palliative management of IPF [174]. Historically, benzodiazepines have been used for managing dyspnoea, but a Cochrane review of 214 participants with varied chronic diseases showed no benefit of benzodiazepines in ameliorating breathlessness. However, conclusions are limited due to the heterogeneity of studies with a limited number of participants [175].

Cough is present in >80% of IPF patients and an independent predictor of progression in IPF [176]. The pathophysiology and mechanism of cough in IPF is complex and poorly understood and treatment includes the management of comorbidities that can influence cough, such as gastro-oesophageal reflux disease (GORD) [176]. Opioid therapies significantly ameliorate cough and are associated with an improved quality of life [177]. However, the therapeutic impact of opioids on reducing cough is extrapolated from its positive findings in chronic cough patients, and there is limited evidence regarding the safety and efficacy of opioids for the management of cough in the terminal stages and palliative treatment of IPF. Drugs specifically targeting cough in IPF have included thalidomide. Due to its immunomodulatory and anti-inflammatory effects, thalidomide was evaluated in a double-blinded, placebo-controlled trial in patients with IPF and cough. This 24-week cross-over trial in 23 IPF patients revealed that thalidomide significantly reduced cough visual analogue scores and cough-specific quality of life measures compared to placebo [178, 179]. However, thalidomide-treated patients experienced more adverse events compared to placebo (77% *versus* 22%). The occurrence of these adverse events and the small sample size has limited its use in cough, and thus larger trials are required to further prove it safety and efficacy. Anecdotally, some IPF patients feel their cough is improved with antifibrotic therapy. In an open-label 12-week study of cough in IPF, the antifibrotic pirfenidone has been shown to reduce objective cough measurements with 24 h cough counts, as well as subjective improvements in cough visual analogue scores. However, this study was not a placebo-controlled study, thus reflecting the limitations of the study [180].

Future novel agents include a pilot study of nebulised sodium cromoglicate (PA101) in IPF reporting to be effective in patients with chronic cough [181]. Currently, an ongoing phase 2b trial was initiated to assess the potential role of inhaled cromolyn sodium (RVT-1601, formerly PA101B) in the therapy of persistent chronic cough in IPF (NCT03864328).

Treatment of comorbidities

While IPF is the main reason for death in patients suffering from this chronic disease, the cause of death in 30–40% of these patients is related to other conditions, *i.e.* comorbidities [182]. Cardiovascular and thromboembolic disorders, GORD, depression, sleep disorders, pulmonary hypertension, emphysema, diabetes and lung cancer are the most common comorbidities in IPF [183]. This association might be explained partially by the elderly population, which is mainly affected by IPF [184]. Yet, many comorbidities worsen the prognosis of the disease [185, 186], reflected by a recent comorbidome (figure 2) illustrating the association of frequencies and groups of diseases to prognosis.

Several studies have focused on the relationship between comorbidities and the burden of disease [85, 187–190]. The German INSIGHTS IPF registry has determined that an increased number of comorbidities decreases HRQL [191]. Recently, the novel comorbidity assessment TORVAN model has shown that comorbidities may refer to a lower survival rate based on clinical and physiological parameters as in the GAP index [192]. While no effects of antifibrotic drugs on comorbidities have been reported so far, several reports focused on the effects of comedications or treatments of comorbidities in IPF. Three studies have reported an association between worsened prognosis and the use of anticoagulants, mainly warfarin, for reasons other than IPF [188, 193, 194]. Recent studies suggested that a new strategy of anticoagulation may have positive effects. Namely, the onset of direct thrombin inhibitors may even show antifibrotic effects that open new avenues in antithrombotic therapy in IPF [195–198]. GORD is a frequent comorbidity in IPF. Based on possible favourable effects of anti-acid therapy on meaningful end-points in IPF, the recent international IPF guideline recommends antacid therapies for all IPF patients. However, owing to newer conflicting data, several national guidelines do not support this recommendation [199–202]. Another approach to GORD in IPF is laparoscopic surgical treatment. Here, a phase II study (WRAP-IPF) showed clinically meaningful impact on lung function and further improvements of other important end-points like respiratory hospitalisations in the group of patients after surgical intervention [203]. Statins reduce cholesterol levels to reduce the risk of cardiovascular morbidity [204, 205]. In addition to their anti-inflammatory effects, they may have a protective effect against smoking and slow down the deterioration of age-associated lung function [206]. In a *post hoc* analysis, IPF patients, who

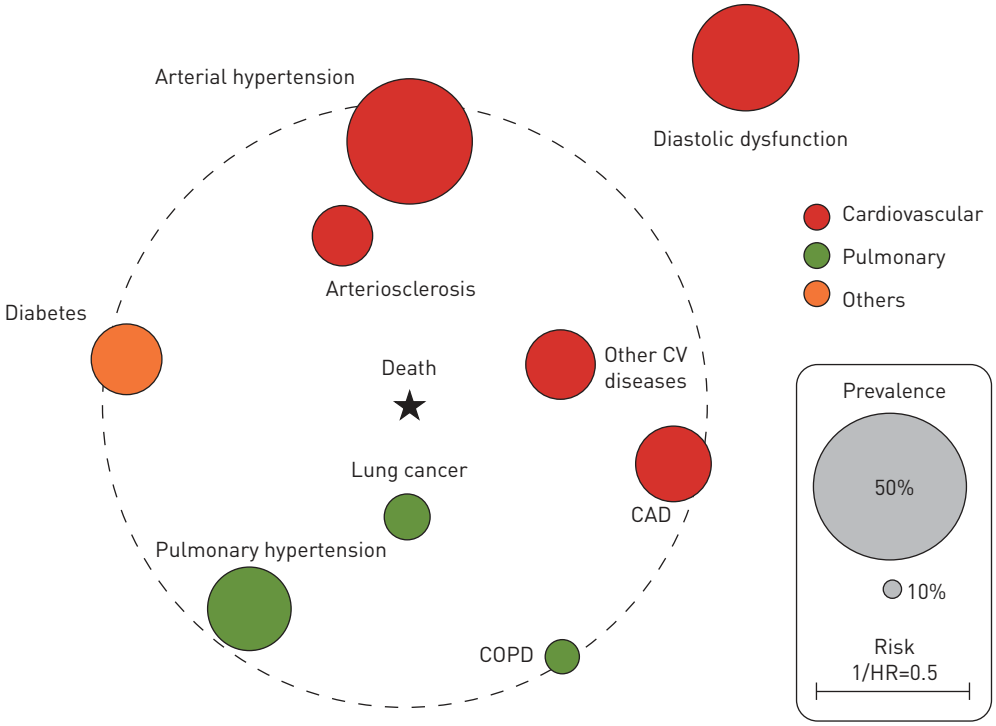

FIGURE 2 Graphic expression (comorbidome) of comorbidities with >10% prevalence in the entire cohort, and those comorbidities with the strongest association with mortality (hazard ratio (HR) >1, 95% CI >1; p<0.05) [166]. The area of the circle relates to the prevalence of the disease. The proximity to the centre (mortality) expresses the strength of the association between the disease and risk of death. This was scaled from the inverse of the HR (1/HR). All bubbles associated with a statistically significant increase in mortality are fully inside the dotted orbit (1/HR <1). Bubble colours represent organ systems or disease clusters. CV: cardiovascular; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease. Reproduced and modified from [186] with permission.

were on statins, had a better prognosis, lower hospitalisation rates, and mortality compared to those who did not receive statin therapy [207, 208]. Also, newest data show some effects of ACE-inhibitors on outcomes in IPF [209].

Urgent unmet need for AE-IPF

AE-IPF is a frequent and severe complication of IPF associated with poor prognosis, especially high hospital mortality [210]. AE-IPF can occur at any time, but is more common in advanced stages of the disease [211]. Idiopathic and triggered, *e.g.* infection-associated, AE-IPF have a similar clinical appearance and outcome [212].

Due to the lack of robust evidence, there is no accepted guideline for the treatment of acute exacerbations, thus practice for AE-IPF varies in different centres [213]. Recently, it was demonstrated in a large international survey that corticosteroids combined with broad-spectrum antibiotics including macrolides are widely used. Yet, doses, duration and route of steroids vary significantly between centres, while only a minority never use steroids. Retrospective data suggest that ECMO has no meaningful effects on the prognosis of patients who are not eligible for lung transplantation [214]. Preventive strategies such as vaccination and antifibrotics are extensively adopted in AE-IPF without clinical evidence [213, 215]. Future research is required to develop strategies for diagnosis, prevention and treatment of AE-IPF.

Conclusions

In recent years, our understanding of the pathophysiology of IPF and potential therapies for IPF have significantly evolved, yet there is still no halt to disease progression and no cure. Future therapies should aim to stabilise the disease, ameliorate symptoms and improve quality of life with the ultimate goal of reducing the burden of disease. Our long-term goal must be to reverse this devastating disease and discover novel ways to cure it, in addition to finding new effective therapies for a major unmet need and the deadliest complication of IPF, acute exacerbations. As such, currently several clinical trials are under way and focusing on new therapeutic approaches. Furthermore, the research field in IPF is expanding to

focus on approaches to improve nonpharmacological therapies to improve quality of life such as rehabilitation, symptom management, enhanced management of comorbidities and a better understanding of the effects of comedications. These advances in research pave the way for an interesting few decades in IPF diagnosis and management.

Conflict of interest: None declared.

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