Pharmacotherapy for idiopathic pulmonary fibrosis: current landscape and future potential

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The landscape of treatment for IPF is on new turf with nintedanib, pirfenidone and new clinical trials
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ABSTRACT Over the past two and a half decades, many clinical trials have been designed to determine the safety and efficacy of pharmacotherapy for patients with idiopathic pulmonary fibrosis (IPF). However, so far, only two drugs (pirfenidone and nintedanib) have been found to have an impact on disease progression as defined by reducing the rate of decline in forced vital capacity over a year among IPF patients with mild to moderate impairment in lung function. These two drugs have been approved for treatment of IPF by regulatory agencies and are currently in clinical use worldwide. This article summarises the current landscape of pharmacotherapy for IPF and highlights the prospects and potential of new therapies that are currently being pursued in clinical trials.

Introduction

The evidence-based 2011 clinical practice guidelines for the diagnosis and management of idiopathic pulmonary fibrosis (IPF) [1] defined IPF as progressive fibrotic lung disease limited to the lungs, occurring in adults without attributable systemic disease and environmental factors. The precise criteria for patterns of usual interstitial pneumonia (the hallmark feature of IPF in the lung) by imaging and histopathology were given in the guidelines. Since then, new evidence has changed the landscape of treatment of IPF and the disease is now being fought on a new turf [2].

Current landscape of pharmacotherapy for patients with IPF

Treatment with antifibrotic agents pirfenidone and nintedanib

The recommendations for pharmacotherapy for patients with IPF was updated in clinical practice guidelines, based on evidence, in 2015 [3]. Conditional recommendations for treatment with two antifibrotic therapies (pirfenidone and nintedanib) and for antiacid treatment were made, acknowledging that the quality of evidence supporting the use of antiacid treatment for IPF was very low, whereas the evidence supporting the use of pirfenidone and nintedanib was based on prospective, randomised clinical trials (RCTs) (table 1). The rate of decline in forced vital capacity (FVC) over 1 year among patients with

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TABLE 1 Comparison of evidence-based treatment recommendations in the 2011 and 2015 guidelines for idiopathic pulmonary fibrosis

Agent	2015 Guideline	2011 Guideline
New and revised recommendations		
Anticoagulation (warfarin)	Strong recommendation against use[#]	Conditional recommendation against use[+]
Combination prednisone+azathioprine +*N*-acetylcysteine	Strong recommendation against use[¶]	Conditional recommendation against use
Selective endothelin receptor antagonist (ambrisentan)	Strong recommendation against use[¶]	Not addressed
Imatinib, a tyrosine kinase inhibitor with one target	Strong recommendation against use[#]	Not addressed
Nintedanib, a tyrosine kinase inhibitor with multiple targets	Conditional recommendation for use[#]	Not addressed
Pirfenidone	Conditional recommendation for use[#]	Conditional recommendation against use[¶]
Dual endothelin receptor antagonists (macitentan, bosentan)	Conditional recommendation against use[¶]	Strong recommendation against use[#]
Phosphodiesterase-5 inhibitor (sildenafil)	Conditional recommendation against use[#]	Not addressed
Unchanged recommendations		
Antiacid therapy	Conditional recommendation for use[+]	Conditional recommendation for use[+]
N-acetylcysteine monotherapy	Conditional recommendation against use[¶]	Conditional recommendation against use[¶]
Antipulmonary hypertension therapy for idiopathic pulmonary fibrosis-associated pulmonary hypertension	Reassessment of the previous recommendation was deferred	Conditional recommendation against use[+]
Lung transplantation: single *versus* bilateral lung transplantation	Formulation of a recommendation for single *versus* bilateral lung transplantation was deferred	Not addressed

Reproduced from [3], with permission from the publisher. [#]: moderate confidence in effect estimates; [¶]: low confidence in effect estimates; [+]: very low confidence in effect estimates.

IPF who had mild to moderately reduced FVC and diffusing capacity of the lung for carbon monoxide (D_{LCO}) measurements at baseline and treated with antifibrotic agents was slower than in patients who were not receiving the antifibrotic agents [4, 5]. However, there was no change in the respiratory symptoms, patient reported outcomes and quality of life associated with treatment with either pirfenidone or nintedanib. Subsequent *post hoc* studies have demonstrated that both pirfenidone and nintedanib have been associated with a reduced rate of decline in FVC, regardless of the severity of disease (as measured by FVC and D_{LCO}) at medication initiation, even when FVC is preserved, mildly decreased and/or severely decreased [6–8]. The 2015 clinical practice guidelines emphasise the need for physicians to discuss both medications with patients, and the decision to initiate one of the medications should be a shared decision based on patient preferred choices, potential benefits and risks, among which side effects are most common [3]. Among the several aspects of the treatment efficacy of nintedanib and pirfenidone that are unknown, it is not yet known whether one agent is more efficacious than the other [9].

Common side effects of pirfenidone include nausea and gastrointestinal upset as well as skin rash and photosensitivity [4]. The most common side effect of nintedanib is diarrhoea, occurring in approximately 60% of patients, but is typically well tolerated with the help of anti-diarrhoeals [5]. Both medications can affect liver function in a small proportion of patients and patients require interval monitoring of their liver function tests throughout treatment. In both the INPULSIS (nintedanib) and ASCEND (pirfenidone) clinical trials, worsening of IPF was noted among adverse events, although this may be difficult to ascertain given the overall clinical course of IPF [1, 4, 5]. Further studies are needed to provide guidance to providers regarding worsening of IPF despite treatment with these agents.

Antiacid treatment for IPF

While acknowledging that no RCTs have determined the safety and efficacy of the use of antiacid for the treatment of IPF, as well as the very low quality of evidence collected to date, the unconflicted members of the committee for IPF that developed the 2015 clinical practice guidelines for pharmacotherapy for IPF recommended a conditional treatment with antiacids for patients with IPF, based on evidence reviewed at the time. Physicians treating patients with IPF must appreciate that the quality of evidence that led the committee to make this recommendation was acknowledged to be low or very low [3]. A subsequent

report of data analysed *post hoc* suggests increased frequency of respiratory infections that were not pre-specified in patients alleged to have received antiacid treatment [10]. However, there are significant concerns regarding the design of that study, and the results must be interpreted with caution [11]. While recent perspectives on the topic discuss the potential and prospects of the antifibrotic properties of proton pump inhibitors (PPIs), several questions regarding the use of PPIs and antiacid treatment need to be answered [11, 12]. In a recent retrospective study, the safety of laparoscopic antireflux surgery in patients with IPF demonstrating abnormal acid gastro-oesophageal reflux (GOR), and a trend to slow the rate of decline in FVC over a year were demonstrated [13]. It is hoped that the ongoing prospective RCT "WRAP-IPF" (ClinicalTrials.gov NCT01982968) will provide useful results and insights regarding the treatment of IPF with surgical correction of abnormal acid GOR or antiacids in patients with IPF.

N-acetylcysteine treatment for IPF

The harmful effects of the triple therapy prednisone plus azathioprine plus *N*-acetylcysteine (NAC) was demonstrated well in the PANTHER-IPF trial [14]. Indeed, this negative study was a major breakthrough in the management of IPF, as this regimen, prior to the results of the trial, was considered a standard of care and first-line treatment for IPF. The regimen has since been eliminated and the standard of care for patients with IPF has improved by avoiding the harmful effects of this triple therapy. The 2015 guidelines for the treatment of IPF made a strong recommendation against the use of this regimen for IPF. The harmful effects were probably due to the immunosuppressive effects of prednisone plus azathioprine, but monotherapy with NAC did not have an effect on disease progression as measured by the rate of decline in FVC, although it demonstrated favourable effects for secondary end-points such as walking distance, D_{LCO} measurements and mental well-being associated with the use of NAC [15]. The 2015 guidelines gave a "conditional" recommendation against its use, which implied the potential benefit of NAC may occur in a minority of patients with IPF [3]. In a subsequent report of the results from the PANORAMA trial [16], which was designed to determine the safety of combined therapy with pirfenidone plus NAC, exploratory analyses from the data gathered suggested no therapeutic potential associated with NAC. Other *post hoc* studies have suggested potential therapeutic effects with NAC monotherapy in a subgroup of patients with genotypes for TOLLIP, and indicate a need for further clinical trials in a precise subgroup of patients with IPF stratified by specific genotypes for treatment with NAC using a pharmacogenomic approach [17]. The potential benefit of NAC monotherapy was observed in IPF patients carrying a particular TOLLIP and not a MUC5B genotype (TOLLIP rs3750920 TT). Thus, the door for the therapeutic potential of the biological plausibility for the antioxidant NAC remains open [18].

Other medications tried for IPF

Multiple other medications with therapeutic potential for IPF based on the biological plausibility of targeting different pathways in the pathogenesis of pulmonary fibrosis and IPF (figure 1) have failed to demonstrate a therapeutic effect. These include interferon gamma, etanercept, imitinib, warfarin, dual and selective endothelin receptor antagonists (bosentan, macitentan and ambrisentan), simtuzumab (a lysyl oxidase inhibitor) [19–25]. Besides the harmful effects of the triple therapy of prednisone plus azathioprine plus NAC, treatment with warfarin and ambrisentan was associated with harmful effects [19, 21]. The ACE-IPF clinical trial [19] was designed to determine the safety and efficacy of warfarin for IPF in patients with IPF, it is unknown if the harmful effects would be the same for patients with IPF who present with thromboembolism and chronic atrial fibrillation, in whom anticoagulation with warfarin would otherwise be indicated. Nevertheless, caution must be used in considering warfarin for patients with IPF for clinical conditions that warrant consideration of the use of warfarin. Treatment with ambrisentan was associated with worsening respiratory decline, regardless of the presence or absence of pulmonary hypertension (PH), and thus is considered an absolute contraindication in patients with IPF who demonstrate significant PH [21].

Treatment with sildenafil, a phosphodiesterase 5 inhibitor, has been tried in a phase II clinical trial for patients with IPF manifesting advanced impairment of lung function, targeting for the probability of coexisting PH in this subset of patients [26]. Although the 6-min walk test distance (the primary end-point generally used to assess treatment response in patients with PH) did not reveal a positive response to treatment with sildenafil, there were significant differences in secondary end-points (improved gas exchange and quality of life), favouring treatment with sildenafil. The 2015 guidelines for the treatment of IPF recommend against (conditional) treatment with sildenafil.

Future pharmacotherapy for IPF

As is clear from the 2015 guidelines, no pharmacotherapy has so far received strong recommendation for the treatment of IPF. The need for medications for the treatment of IPF has been modestly met with the two antifibrotic drugs pirfenidone and nintedanib, and several questions must be answered for all patients

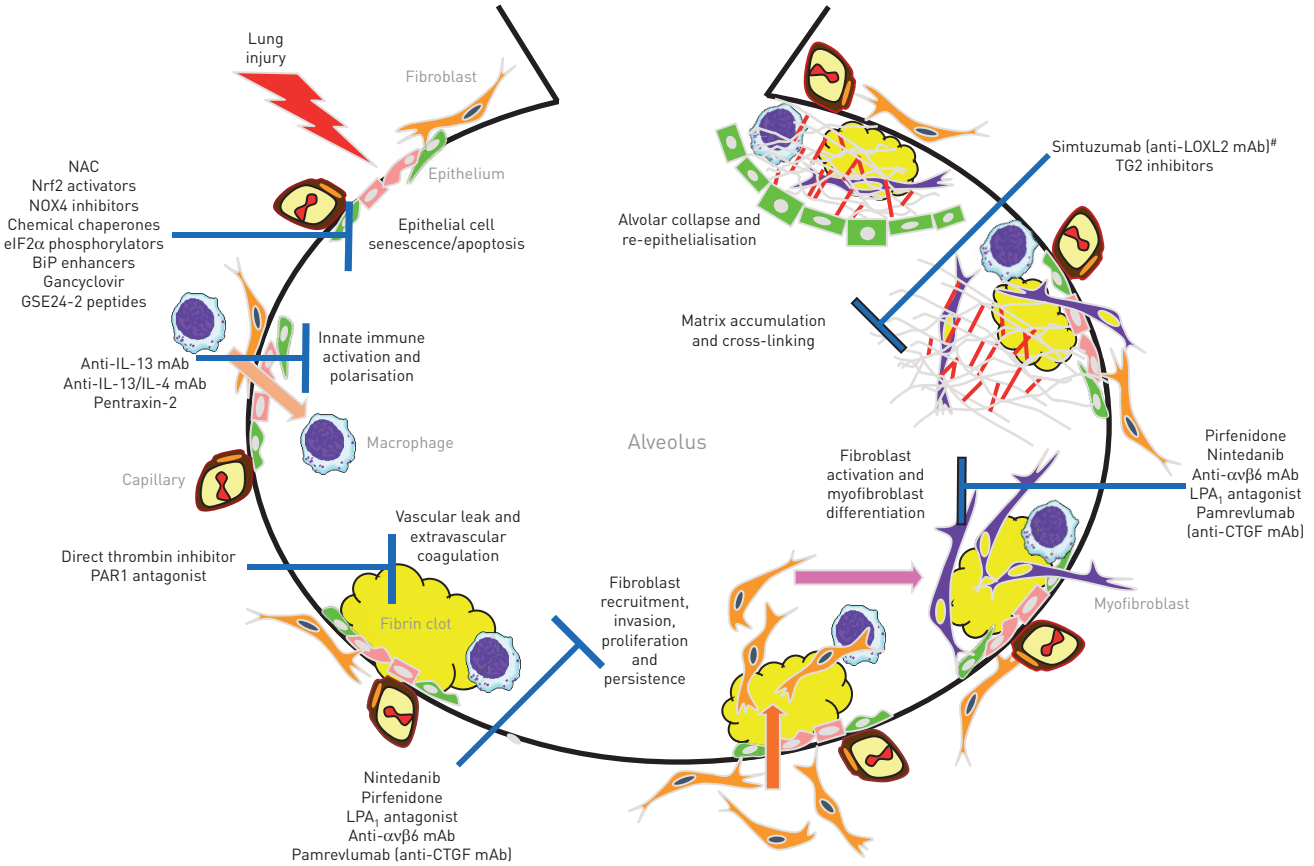

FIGURE 1 Concepts in the pathogenesis of idiopathic pulmonary fibrosis (IPF). Schematic representation and investigational therapies for IPF, targeting aberrant responses to injury. The schematic indicates the sequential profibrotic processes implicated in the currently prevailing paradigm of IPF pathogenesis, in which recurrent or persistent injury to the alveolar epithelium is believed to drive aberrant wound-healing responses, resulting in fibrosis rather than repair. Drug candidates evaluated in recently completed or ongoing phase II and III clinical trials in IPF are placed in the context of the profibrotic process(es) they are believed to target. Although fibrosis in IPF appears to predominantly expand the interstitial compartment, the aberrant repair processes driving IPF progression, and the fibrosis they produce, may occur in both the interstitium and the airspaces. For the purposes of figure clarity, the development of fibrosis in the airspaces is depicted in this figure. #: the recent clinical trial using simtuzumab failed to demonstrate the therapeutic potential of blocking LOXL2 [25]. NAC: *N*-acetylcysteine; IL: interleukin; CTGF: connective tissue growth factor; LOXL2: lysyl oxidase 2. Courtesy of Dr A. Tager; reproduced and modified from [27] with permission from the publisher.

with IPF (*i.e.* its severity, and the extent of the primary disease and comorbid conditions that patients with IPF are known to manifest) [9]. The landscape for the treatment of IPF is clearly on new turf, and stabilisation of the disease process (*i.e.* stall disease progression and reverse the disease process before the pulmonary parenchyma progresses to irreversible honeycombing) must be pursued in new clinical trials.

The lung function tests traditionally used to monitor overall impairment in lung function status and the changes in FVC over 12 months have been accepted as correlates of disease status and survival and accepted by regulatory agencies as indicators of treatment response. However, assessment of treatment response with circulating biomarkers of actual fibrotic processes implicated in the pathogenesis of fibrosis and/or assessment of extent of fibrosis as end-points are needed to determine the modulating effects of an antifibrotic drug. The latter is being assessed by quantifying the anatomical extent of pulmonary fibrosis by imaging patterns in ongoing clinical trials, and it is anticipated this will be investigated further in future clinical trials. In addition to achieving end-points that are biologically plausible and convincingly modulate the local tissue response in the lung, the absolute need to improve outcomes for patients with IPF that are clinically meaningful to them, such as improving symptoms, quality of life and survival, is evident. Indeed, these issues are being pursued in ongoing clinical trials and the results are eagerly anticipated.

There are several ongoing clinical trials for the treatment of IPF (see https://ClinicalTrials.gov). Figure 1 shows a schematic representation of the concepts for the pathogenesis of IPF, developed over several years of research at the bedside and bench, as well as the drugs that have been or are being used in clinical trials to target some of the cascades of the inflammatory–fibrotic cascade [27]. Among the many potential therapeutic targets beyond those that are modulated by nintedanib and pirfenidone, there are some phase II clinical trials that are nearing completion and/or just completed, and the results are eagerly anticipated. Hopefully, the results will yield positive findings and/or signals to pursue phase III clinical trials. These include studies with the serum amyloid protein pentraxin 2, a member of the pentraxin family that stops or reverses fibrosis in multiple organ systems [28]. Recombinant human pentraxin 2 (PRM-151), targeting the innate immune pathway in the pathogenesis of pulmonary fibrosis/IPF, has been shown to be safe in phase I studies at all dose levels tested, and FVC measurements and the 6-min walk distance trended towards improvement in early clinical trials [29]. The results of the PROMOTE phase II trial (studying PRM-151) are eagerly anticipated. Another novel approach that has been undertaken is to block the interleukin (IL)-4 and IL-13 pathways. An ongoing phase II clinical trial, designed to determine the safety and efficacy of an engineered humanised bi-specific antibody (SAR 156597) targeting these two specific cytokines, is hoped to yield positive results. Encouraging results from the open-label phase II clinical trial targeting connective tissue growth factor (CTGF) [30] have been pursued in an ongoing placebo-controlled phase II clinical trial (PRAISE) with the hope of conducting phase III clinical trials to determine the safety and efficacy of intravenous infusions of monoclonal antibody against CTGF (pamrevlumab) as an antifibrotic treatment for IPF.

Other treatment modalities that need to be investigated include the treatment of comorbidities, such as the modulation of vasculopathy, as PH is a well-known sequela of persisting pulmonary fibrosis. In this regard, the safety of the phosphodiesterase inhibitor sildenafil and the dual endothelin receptor antagonists macitentan and bosentan has been demonstrated in patients with IPF, and the recommendation against treatment with these agents for PH associated with IPF was conditional [3]. Because several patients with IPF do manifest PH, even in patients with minimum or no honeycombing, combination therapies with existing and/or new treatment with these agents are warranted. In this regard, it is hoped that the ongoing clinical trial using combined nintedanib and sildenafil will yield positive results.

Other novel treatment approaches being pursued include the use of antibiotics, addressing the concept of the lung microbiome in the pathogenesis of IPF (the design for the CleanUp-IPF trial is under way). Newer strategies with pharmacogenomics (such as the use of NAC stratified by the MUC5b and TOLLIP genotypes), relaxin-based therapy [31], the lengthening of telomeres in a subgroup of patients with shortened telomeres and/or *TERT*/*TERC* mutations [32] are among future strategies for precision medicine in patients with IPF.

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