Clinical trials in idiopathic pulmonary fibrosis: where we have been and where we are going

Fabrizio Luppi · Paolo Spagnolo · Stefania Cerri · Giacomo Sgalla · Luca Richeldi

Published online: 23 September 2012
© Springer Science+Business Media, LLC 2012

Abstract Idiopathic pulmonary fibrosis (IPF) is the most common and most lethal diffuse fibrosing lung disease, with an increasing incidence and a mortality rate that exceeds that of many types of cancer. At present, there is no effective standard treatment recommended by guideline documents. As such, the unmet medical need is high. Recently, several high-quality clinical trials, evaluating safety and efficacy of different novel molecules, have been concluded. The results have mostly been disappointing, although some compounds have shown promising results. In particular, pirfenidone seems to be the most advanced molecule for IPF treatment, having been approved in Europe, Japan and India. Nintedanib, a triple kinase inhibitor, has almost completed enrolment of Phase III trials, based on promising Phase II results. Randomized controlled trials still represent a valid choice for IPF patients, and their completion is critically important to achieving the ultimate goal of curing IPF. Future approaches will probably include the evaluation of currently available agents alone and in combination, the identification of novel drugs with pleiotropic actions, and trials with validated, weighted composite endpoints.

Keywords Idiopathic pulmonary fibrosis · Clinical trials · Pirfenidone · Nintedanib · Endpoint

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown

cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP) [1]. IPF follows a variable clinical course in which periods of relative stability are punctuated by episodes of accelerated decline, often resulting in respiratory failure and death; this identifies various IPF phenotypes, thus making the natural history of the disease largely unpredictable in the individual patient [2]. Nevertheless, IPF has been reported as the primary cause of death in 89 % of patients who died in a cohort of 168 IPF patients in the placebo group of a large randomized trial [3]. In the past, the hypothesis that IPF started as an inflammatory alveolitis led to the use of anti-inflammatory and immunosuppressive drugs; in line with this etiopathogenetic concept, previous IPF guidelines recommended corticosteroids in addition to cytotoxic agents (azathioprine or cyclophosphamide) as the standard treatment [4], although this recommendation was supported by a very low level of evidence (i.e., low quality and limited number of studies). As of today, no standard treatment is recommended by the recent evidence-based guidelines [1]. However, several recent high-quality clinical trials, evaluating a number of novel therapies, have been completed. As such, it is conceivable that these recommendations might be partly updated in the near future. The results of these trials have mostly been disappointing, although some compounds have shown promising results. In particular, pirfenidone seems to be the most advanced molecule for IPF treatment, having been approved in Europe, Japan and India. In general, due to the complexity and the uncertainties intrinsic to IPF, it is essential that each therapeutic strategy be tailored to the individual patient, after discussing the potential benefits and pitfalls. Randomized controlled trials still represent a valid choice for IPF patients, and their completion is critically important to achieving the ultimate goal of curing IPF.

F. Luppi · P. Spagnolo · S. Cerri · G. Sgalla · L. Richeldi (✉)
Center for Rare Lung Diseases, University Hospital of Modena,
Via del Pozzo 71,
41124 Modena, Italy
e-mail: luca.richeldi@unimore.it

This review aims at describing the major trials performed so far, outlined in Table 1, regardless of their experimental phase, the lesson learnt from them and the challenges in the implementation of these results in clinical practice and guidelines, with emphasis on the choice of appropriate endpoints.

Phase II trials

Tyrosine kinase inhibitors

A recently completed Phase II clinical trial focused on the potential of inhibiting tyrosine kinase receptors, a therapeutic approach widely explored in oncology. Tyrosine kinases regulate a variety of physiological cell processes, including metabolism, growth, differentiation and apoptosis, and aberrant tyrosine kinase activity has been shown to promote the development and progression of both neoplastic and non-neoplastic diseases [5, 6]. Signaling pathways activated by tyrosine kinases have also been suggested to be involved in lung fibrosis [7]. This, in turn, has prompted clinical trials evaluating the efficacy of tyrosine kinase inhibitors in IPF.

Nintedanib

The TOMORROW (To Improve Pulmonary Fibrosis With BIBF 1120) study, a 12-month, randomized, double-blind, placebo-controlled trial, evaluated the safety and efficacy of nintedanib (BIBF 1120) [8], an intracellular inhibitor of at least three tyrosine kinase receptors [platelet-derived growth factor (PDGF) receptors α and β , vascular endothelial growth factor (VEGF) receptors 1, 2, and 3, and fibroblast growth factor

(FGF) receptors 1, 2, and 3] [9]. Four different oral doses of this drug (50 mg once a day, 50 mg, 100 mg, or 150 mg all twice a day) have been tested. The primary end point of the study was the annual rate of decline in forced vital capacity (FVC). Secondary endpoints included acute exacerbations, quality of life and total lung capacity. Nintedanib at a dose of 150 mg twice daily showed a trend toward a reduction in the decline in lung function, with fewer acute exacerbations and preserved quality of life, as compared with the placebo arm. Specifically, in the group receiving 150 mg of nintedanib twice a day, FVC declined by 0.06 liters per year, as compared with 0.19 liters per year in the placebo group, a 68.4 % relative reduction in the rate of loss. In addition, patients treated with the higher dose of this drug experienced a lower incidence of acute exacerbations and a small decrease in St. George's Respiratory Questionnaire (SGRQ) score (as compared with an increase with placebo, meaning a better or preserved quality of life in treated patients). Nintedanib showed an acceptable safety profile. In fact, while gastrointestinal side effects (diarrhea, nausea, and vomiting) and increases in levels of liver aminotransferases were more frequent in the group receiving 150 mg twice daily than in the placebo group, severe adverse events occurred with similar frequency in the placebo and in the four active treatment groups. These results warranted the investigation of this kinase inhibitor in two concomitant Phase III clinical studies, with results expected in late 2013.

Imatinib

Imatinib is a tyrosine kinase inhibitor with activity against several fibrogenic factors (including PDGFR- α and β), which has been investigated in IPF based on encouraging data from

Table 1 Major recent RCTs performed in patients with IPF

Author, year	Drug evaluated	Experimental phase	Number of patients enrolled
Azuma, 2005	Pirfenidone	2	109
Kubo, 2005	Warfarin	2	56
Demedts, 2005	Prednisone, azathioprine, N-acetylcysteine	2	155
King, 2008	Bosentan	3	154
Raghu, 2008	Etanercept	2	88
King, 2009	Interferon-gamma	3	826
Daniels, 2010	Imatinib	2	121
Taniguchi, 2010	Pirfenidone	3	267
Zisman, 2010	Sildenafil	2	180
Noble, 2011	Pirfenidone	3	779
King, 2011	Bosentan	3	616
Richeldi, 2011	Nintedanib	2	428
Noth, 2012	Warfarin	3	145
IPFnet, 2012	Prednisone, azathioprine, N-acetylcysteine	3	155

animal models of lung fibrosis. Imatinib has been shown to inhibit lung fibroblast-myofibroblast transformation and proliferation, as well as extracellular matrix production through inhibition of PDGF and TGF- β signaling [10]. In a Phase II, randomized, double blind, placebo-controlled study, 119 IPF patients enrolled in 13 centers in the United States and Mexico were randomly assigned to receive imatinib (600 mg orally once daily) or placebo for 96 weeks [11]. Patients were eligible if they had had clinical worsening within the past year as demonstrated by any one of the following: ≥ 10 % decrease in FVC % predicted, worsening chest X-ray, or worsening dyspnea at rest or on exertion. This trial specifically aimed to study patients with “mild or moderate” IPF. The primary outcome was a combined measure of disease progression defined as a ≥ 10 % decline FVC from baseline or death. Secondary endpoints included change from baseline in diffusing capacity of the lung for carbon monoxide (DLCO) % predicted, change from baseline in the resting arterial blood gas assessment of A-a gradient, change in the number of meters walked in a 6-min walk distance (6MWD), change from baseline in the SGRQ assessments and overall mortality, all evaluated after 96 weeks. No differences in the predefined primary or secondary end points were observed between the imatinib and the placebo groups. Serious adverse events occurred at similar rates in the two study groups. Based on these results, it seems unlikely that imatinib will be further explored in the treatment of IPF.

TNF-alpha receptor inhibitors

Elevated levels of tumor necrosis factor (TNF)-alpha, a cytokine with inflammatory and fibrogenic properties, have been detected in the lungs of animals in experimental models of pulmonary fibrosis [12], and in patients with IPF [13]. A fibrosing alveolitis develops in transgenic mice expressing high TNF-alpha levels in their lungs [14], and adenoviral transfer of TNF-alpha complementary DNA to lungs of normal adult rats results in the increased transforming growth factor (TGF)-beta expression, followed by the development of fibrosis [15]. Furthermore, in animal models of pulmonary fibrosis, TNF-alpha antagonists inhibit pulmonary inflammation and fibrosis [16], suggesting that such agents could potentially diminish the fibrotic response in the lungs of patients with IPF.

Etanercept

In a 48-week, randomized, double blind, placebo-controlled, multicenter, Phase II trial, Raghu and coworkers evaluated safety and efficacy of subcutaneous (25 mg twice weekly) etanercept, a soluble TNF-alpha receptor antagonist that is used to treat rheumatoid arthritis, in subjects with IPF [17]. No significant differences in primary endpoints (changes in FVC % predicted, DLCO % predicted, and oxygenation at rest) were observed between the groups. However, a trend towards a

benefit in the etanercept group was observed with regard to several physiologic, functional, and quality-of-life endpoints among subjects receiving the drug. There was no difference in adverse events between treatment groups, demonstrating the drug is safe. Because this study included a relatively small ($n=88$) number of patients, the authors suggested that this could account for the lack of statistically significant differences between treatment groups in the primary endpoints. In fact, based on the observed means and pooled standard deviation, a 3.5-fold greater sample size would have been required for the between-group differences observed in this study to be statistically significant. Of note, during the 48 weeks of the trial, almost 25 % of patients withdrew from the study, similar to the dropout rates seen in other trials [18, 19], which represents an intrinsic potential issue inherent to long-term trials in IPF.

Phase III trials

N-acetylcysteine

In the IFIGENIA (Idiopathic Pulmonary Fibrosis International Group Exploring N-Acetylcysteine I) trial [18], Demedts and coworkers showed that the addition of N-acetylcysteine (NAC) to what was considered to be the standard therapy, i.e. prednisone and azathioprine combined, significantly slowed the rate of deterioration of the primary endpoints of the study, i.e. vital capacity (VC) and DLCO, as compared to prednisone and azathioprine alone. A relative difference of 24 % was observed for DLCO and of 9 % for VC. The results of this trial deserve attention for a number of reasons. Firstly, the lack of a true placebo arm, although patients treated with prednisone and azathioprine in the IFIGENIA trial experienced a decline in FVC similar to the one observed in the placebo group of other large trials [19–21]. This comparison would suggest that prednisone combined with azathioprine is no better than placebo in preserving lung function in patients with IPF. Secondly, the reduction in the decline of VC and DLCO in the NAC arm did not translate into a survival benefit (although with the limitations intrinsic to the study design of a 1-year trial). Thirdly, the drop-out rate (about 30 %) was much higher than in previous IPF trials: as a direct consequence, the statistics utilized, the least squares last observation carried forward (LS-LOCF), was one preserving the sample size from the high drop-out rate, but with the risk of making unwarranted assumptions about the missing data, resulting in either underestimating or overestimating the treatment effects.

To further investigate the possible efficacy of NAC in patients with IPF, the National Heart, Lung and Blood Institute sponsored a three-arm placebo-controlled trial designed and carried out by the IPFnet consortium, the PANTHER-IPF (Prednisone, Azathioprine, and N-acetylcysteine: A Study That Evaluates Response in IPF) study, in which patients with

mild to moderate lung function impairment were randomized in a 1:1:1 ratio to prednisone, azathioprine and NAC (combination therapy), NAC alone or placebo. Primary outcome was the change in longitudinal FVC measurements over a 60-week period. Secondary outcomes included mortality, time to death, frequency of idiopathic acute exacerbations, and time to disease progression as defined by composite endpoint of death or relative drop in FVC ≥ 10 %. A pre-specified efficacy and safety interim analysis, planned at approximately 50 % of data collection, unexpectedly showed that the combination therapy, as compared to placebo, was associated with a statistically significant increase in all cause mortality (11 % vs. 1 %), all-cause hospitalizations (29 % vs. 8 %), and treatment-related severe adverse events (31 % vs. 9 %). These observations, coupled with no evidence of physiological or clinical benefit for combination therapy, prompted the independent data and safety monitoring board to recommend termination of the combination therapy group at a mean follow-up of 32 weeks [22]. The NAC and the placebo arms of this trial recently completed enrollment and the final results of the PANTHER study are expected in late 2013. These data will allow answering the fundamental question of whether NAC slow the rate of progression in IPF, but the published interim analysis of this trial already contributed the crucial information that a combination of corticosteroid and immunosuppressor does not provide benefit in this disease. Considering that this regimen has been the recommended standard of care for IPF for more than a decade, these findings should be regarded as groundbreaking and underline the relevance of basing clinical practice on the evidence from properly designed randomized clinical trials.

Interferon-gamma

In 1999, in a small open-label trial, Ziesche and coworkers showed that interferon (IFN)-gamma 1 beta (an endogenous cytokine with anti-fibrotic and immunomodulatory effect) significantly improved different clinical markers as compared to placebo [23]. This study formed the basis for a large, multicenter, randomized, placebo-controlled trial in which 330 IPF patients (who had failed to respond to a course of corticosteroids) were randomized to subcutaneous IFN-gamma or placebo [21]. While no significant differences were observed in the primary outcome of progression-free survival or the secondary outcomes of pulmonary function or quality of life, there was a statistical trend toward lower mortality in the treated group. Moreover, in a post-hoc analysis of subjects with a baseline FVC greater than 55 % predicted, there were significantly fewer deaths seen in the IFN-gamma arm (4.8 % vs. 16.4 % in the placebo group); a similar finding was observed for the group with a baseline DLCO greater than 30 % predicted (3.4 % vs. 13.2 % of placebo). However, a subsequent large randomized-controlled trial of over 800

patients with mild to moderate IPF (the INSPIRE trial, International study of Survival outcomes in idiopathic Pulmonary fibrosis with InteRfEron gamma-1b) was stopped after the statistical analysis of data in a predefined interim analysis excluded the possibility that IFN-gamma treatment might result in a significant reduction of the risk of death [24]. On the other hand, IFN-gamma therapy was associated with severe side effects, and it has been suggested that it may in fact worsen the disease course in patients with lower FVC values, and possibly in those with a familial form of the disease [25, 26]. This latter study performed remains the only large clinical trial so far exploring the effect of a treatment on overall survival as primary outcome, rather than on surrogate markers (i.e. lung function), and it has been very informative on the natural history of the disease, if one looks at the data from the placebo arm. Nonetheless, both IFN-gamma trials disappointingly provided negative findings. However, the IFN-gamma epithelial lining fluid (ELF) levels after subcutaneous administration of the drug are unknown. In fact, in a previous study [27], subcutaneous administration of maximally tolerated amounts of recombinant IFN-gamma (250 micrograms) was followed by detectable levels of IFN-gamma in serum, but not in the ELF [27]. Following inhalation, IFN-gamma is not detectable in serum, but it is detectable in respiratory ELF in a dose-dependent fashion, thus suggesting that the administration route could impact efficacy of the drug in the lung. Furthermore, at least in a small study, a beneficial effect of IFN-gamma was observed on individual patients [28]. Although these findings may suggest that in few selected patients IFN-gamma might actually slow disease course, this treatment is strongly discouraged in patients with IPF.

Endothelin-receptor antagonists

Bosentan

In 2008, King and coworkers [19] published the BUILD-1 (Bosentan Use in Interstitial Lung Disease) trial, which enrolled 148 patients randomized to receive bosentan, an endothelin ET_A and ET_B receptor antagonist approved for the treatment of pulmonary arterial hypertension [29], or placebo. The primary endpoint was change from baseline up to 12 months in 6MWD. Twenty-two of 74 patients in the bosentan group and 23 of 84 in the placebo group discontinued treatment. There was no effect of bosentan on the primary endpoint of 6MWD, and there was no impact on the rate of decline of FVC. However, a trend in favor of bosentan was observed in the secondary endpoint of time to death or disease progression. Interestingly, when the subset of patients that had undergone a diagnostic surgical lung biopsy was analyzed separately in a *post hoc* analysis, there was a difference in favor of bosentan in preventing disease progression. Changes from baseline in assessments of

dyspnea and quality of life also favored bosentan in this subgroup. Based on this non-predefined subset analysis (i.e., IPF patients with a surgical lung biopsy), the BUILD-3 trial was designed, but it also failed meeting the primary endpoint, which was time to IPF worsening or all-cause death up to end of study. Taken together, these data support neither the use of bosentan in treatment of IPF regardless of the presence of pulmonary hypertension (possibly this drug is unlikely to impact on both fibrogenesis and pulmonary hypertension secondary to pulmonary fibrosis), nor further studies evaluating this compound in this specific disease.

Ambrisentan

Ambrisentan is a selective antagonist of the ET_A receptor, approved for the treatment of pulmonary arterial hypertension [30]. ET_A receptor also exerts pro-fibrotic activities through the stimulation of transforming growth factor- β and promoting epithelial-to-mesenchymal transition [21]. Importantly, evidence from preclinical models showed that the phenotypic and transcriptional responses to ambrisentan are different from bosentan, thus suggesting that clinical effects in IPF may also be different [22]. The ARTEMIS-IPF (Randomized, Placebo-Controlled Study to Evaluate Safety and Effectiveness of Ambrisentan in IPF) trial was a randomized, double-blinded, placebo-controlled, multinational trial evaluating effectiveness of ambrisentan in reducing the rate of progression of IPF. The results of this study have not been published in full in a peer-reviewed journal; however, the trial has been prematurely stopped following an interim analysis of unblinded efficacy and safety by the Study Data Monitoring Committee indicating a very low likelihood of efficacy for the primary endpoint of disease progression and a likely increase in disease progression for patients in the active arm (http://www.gilead.com/pr_1510358, December 22, 2010).

Sildenafil

In a double blind, randomized, placebo-controlled trial, the phosphodiesterase-5 inhibitor sildenafil was studied during two periods in patients with IPF [31]. The first period consisted of 12 weeks of a double-blind comparison between sildenafil and placebo. The primary outcome was the proportion of patients with an increase in the 6MWD of 20 % or more. Key secondary outcomes included changes in oxygenation, degree of dyspnea, and quality of life. The second period was a 12-week open-label evaluation involving all patients receiving sildenafil. A total of 180 patients were enrolled. The study did not meet the primary outcome, with nine of 89 patients (10 %) in the sildenafil group and six of 91 (7 %) in the placebo group having an improvement of 20 % or more in the 6MWD (i.e. the pre-defined primary

outcome). However, there were small but significant differences in arterial oxygenation, carbon monoxide diffusion capacity, degree of dyspnea, and quality of life favoring sildenafil. Serious adverse events were similar in the two study groups. The presence of some positive secondary outcomes certainly creates clinical equipoise for further research on this molecule in IPF.

Pirfenidone

Four placebo-controlled randomized trials [20, 32, 33] explored the effect of pirfenidone on the decline of pulmonary function, as measured by means of decrease in FVC or VC, although this outcome was a secondary endpoint in one study [32]; three of them [20, 33] also assessed the effect on progression-free survival. The combination of the estimates of these three studies showed that pirfenidone reduced the risk of disease progression by 30 % [34]. Exploring the two studies performed on Caucasian patients [20], an efficacy dose-response relation was observed in one study. In the other one, no significant differences were noted between the pirfenidone and placebo groups on the primary outcome, i.e. the percentage predicted FVC change at week 72. Analyses of pooled data for the two studies supported a pirfenidone treatment effect on percentage predicted FVC, progression-free survival, and 6MWT distance [20]. The discrepancy in the results of these two trials seems virtually impossible to be convincingly explained. Despite identical inclusion criteria for both trials, the authors hypothesized that these controversial results could be accounted for by intrinsic IPF heterogeneity in terms of disease course and outcome. However, the recent approval in Europe of pirfenidone for mild to moderate IPF corroborates the potential for a role of this drug in IPF treatment. On the other hand, the US Food and Drug Administration has declined approval of pirfenidone for treatment of IPF and asked for additional evidence of efficacy. As such, another Phase III randomized, double-blinded, placebo-controlled, trial (Assessment of Pirfenidone to Confirm Efficacy and Safety in IPF: the ASCEND trial) is currently enrolling patients in the US. Current evidence-based IPF guidelines, considering the cost of therapy and the potentially relevant side effects expressed a weak recommendation against the use of this drug. However, it has to be noted that the majority of panel experts abstained in this specific voting [1].

Anticoagulants

Inflammation and vascular injury have been proposed to contribute to a pro-thrombotic state in IPF [35]. Based on this pathogenic hypothesis, 56 Japanese patients with IPF were randomly assigned to prednisolone alone or prednisolone plus anticoagulation (unfractionated or low-molecular-

weight heparin during follow-up when re-hospitalized, and warfarin during outpatient treatment) in an unblinded study [36]. While the incidence of acute exacerbations did not differ between the groups, the mortality associated with acute exacerbation was significantly reduced in the anticoagulant group compared to that in the non-anticoagulant group (18 % vs. 71 %, respectively; $p=0.008$). In turn, this translated in a significant improvement in survival at 3 years (63 % in the anticoagulant group compared with 35 % in the non-anticoagulant group). Several methodological issues raise concerns regarding this study: absence of blinding; incidence of acute exacerbation higher than usually observed (64 % in the placebo group); patient recruitment on initial hospitalization, thus there may have been a selection bias toward more advanced and rapidly progressive disease; substantial withdrawals of patients in the anticoagulant group after randomization but before initiating treatment, therefore, it cannot be excluded that patients who withdrew were more ill and would have had higher mortality; failure to exclude pulmonary embolism as a potential cause of acute deterioration. As such, treatment with anticoagulants has not been recommended for routine use in patients with IPF (weak recommendation, very low-quality evidence) [1]. Recently, the Anticoagulant Effectiveness in Idiopathic Pulmonary Fibrosis (ACE-IPF) trial, designed and completed by the IPFnet in the US, tested the hypothesis that warfarin would reduce rates of mortality, hospitalization, and decline in FVC [37]. In this double blind, placebo-controlled trial patients were randomly assigned in a 1:1 ratio to warfarin or matching placebo for a planned treatment period of 48 weeks. Due to a low probability of benefit and an increase in mortality observed in the subjects randomized to warfarin (14 warfarin vs. 3 placebo deaths; $p=0.005$), the independent Data and Safety Monitoring Board recommended stopping the study after 145 of the planned 256 subjects were enrolled (72 warfarin, 73 placebo). Similar trends in the warfarin arm were observed in all-cause hospitalization, respiratory-related hospitalization, and acute exacerbation of IPF. In partial accordance with the current guideline recommendations, the results of this study strongly argue against the routine use of warfarin for the treatment of IPF. As such, recommendations on this drug are very likely to change in the near future.

Conclusion: where we are going

The past decade has witnessed an impressive escalation in the number and the quality of clinical trials undertaken and completed in IPF. The outcome of most of these trials has been disappointing overall, with only a few exceptions. Despite this fact, valuable insights about the pathogenesis, the natural history and the clinical course of

this deadly disease have been gained from the well-characterized cohorts of patients enrolled into these trials. As mentioned above, the recommendations of the current evidence-based guidelines reflect the concept that pharmacological treatment does not appear to impact on natural history of IPF. There are various possible explanations for this fact. Firstly, IPF heterogeneity, which implies pooling of patients with various degree of progression, may have played a major role, particularly before the recent evidence-based diagnostic criteria were established. It is conceivable that the efficacy of any given therapy might similarly be variable, based on the unique phenotypic characteristics and the stage of the disease. Indeed, the heterogeneous nature of IPF and probable varied response to different therapies might partially explain the negative results and mixed signals seen from many of the clinical trials performed thus far. Secondly, the still largely incomplete knowledge of the mechanisms of IPF prevents from choosing disease-specific treatments. Based on current pathogenetic concepts, the ideal agent to treat IPF should target a redundancy of molecular mechanisms. In this regard, the therapeutic approaches that have demonstrated some evidence of efficacy are multi-mechanistic in their action. Thirdly, the choice of primary endpoints and study design did reveal as a major challenge. Retrospective analyses of large placebo-controlled trials and clinical cohorts indicate that a decline of ≥ 10 % in FVC over 6 to 12 months does predict subsequent mortality [38–40]. However, there is an ongoing scientific debate on whether FVC is a valid surrogate for mortality in IPF [41, 42], with the final answer probably coming from adequately powered future trials. Optimal study duration is unknown, with most studies exploring the effects of treatments over an arbitrary 12 months period. In addition, all the studies whose rationale derived from data obtained from non-prespecified post-hoc analysis have failed to meet their respective endpoints, highlighting the intrinsic risks of designing trials based on post hoc statistical analyses in such a heterogeneous disease. Finally, future approaches should include the evaluation of currently available agents alone and in combination, the identification of novel drugs with pleiotropic actions, and trials with validated, weighted composite endpoints. Further genomic signature differentiation and validation may, in the future, enable study enrichment with IPF patients at highest risk of progression and mortality, thus allowing the design of more cost-effective trials.

Disclosure F. Luppi: none; P. Spagnolo: none; S. Cerri: none; G. Sgalla: none; and L. Richeldi: consultant (Boehringer Ingelheim, InterMune, GlaxoSmithKline, Gilead, and Sanofi-Aventis).

References

- Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011;183(6):788–824.
- King Jr TE, Pardo A, Selman M. Idiopathic pulmonary fibrosis. *Lancet*. 2011;378(9807):1949–61.
- Martinez FJ, Safrin S, Weycker D, Starko KM, Bradford WZ, King Jr TE, et al. The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med*. 2005;142(12 Pt 1):963–7.
- American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med*. 2000;161(2 Pt 1):646–64.
- Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. *N Engl J Med*. 2008;358(11):1160–74.
- Grimminger F, Schermuly RT, Ghofrani HA. Targeting non-malignant disorders with tyrosine kinase inhibitors. *Nat Rev Drug Discov*. 2010;9(12):956–70.
- Beyer C, Distler JH. Tyrosine kinase signaling in fibrotic disorders: Translation of basic research to human disease. *Biochim Biophys Acta*. 2012 (Epub ahead of print)
- Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med*. 2011;365(12):1079–87.
- Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. *Cancer Res*. 2008;68(12):4774–82.
- Daniels CE, Wilkes MC, Edens M, Kottom TJ, Murphy SJ, Limper AH, et al. Imatinib mesylate inhibits the profibrogenic activity of TGF-beta and prevents bleomycin-mediated lung fibrosis. *J Clin Invest*. 2004;114(9):1308–16.
- Daniels CE, Lasky JA, Limper AH, Mieras K, Gabor E, Schroeder DR. Imatinib treatment for idiopathic pulmonary fibrosis: Randomized placebo-controlled trial results. *Am J Respir Crit Care Med*. 2010;181(6):604–10.
- Thrall RS, Vogel SN, Evans R, Shultz LD. Role of tumor necrosis factor-alpha in the spontaneous development of pulmonary fibrosis in viable motheaten mutant mice. *Am J Pathol*. 1997;151(5):1303–10.
- Kapanci Y, Desmouliere A, Pache JC, Redard M, Gabbiani G. Cytoskeletal protein modulation in pulmonary alveolar myofibroblasts during idiopathic pulmonary fibrosis. Possible role of transforming growth factor beta and tumor necrosis factor alpha. *Am J Respir Crit Care Med*. 1995;152(6 Pt 1):2163–9.
- Miyazaki Y, Araki K, Vesin C, Garcia I, Kapanci Y, Whitsett JA, et al. Expression of a tumor necrosis factor-alpha transgene in murine lung causes lymphocytic and fibrosing alveolitis. A mouse model of progressive pulmonary fibrosis. *J Clin Invest*. 1995;96(1):250–9.
- Sime PJ, Marr RA, Gauldie D, Xing Z, Hewlett BR, Graham FL, et al. Transfer of tumor necrosis factor-alpha to rat lung induces severe pulmonary inflammation and patchy interstitial fibrogenesis with induction of transforming growth factor-beta1 and myofibroblasts. *Am J Pathol*. 1998;153(3):825–32.
- Piguet PF, Vesin C. Treatment by human recombinant soluble TNF receptor of pulmonary fibrosis induced by bleomycin or silica in mice. *Eur Respir J*. 1994;7(3):515–8.
- Raghu G, Brown KK, Costabel U, Cottin V, du Bois RM, Lasky JA, et al. Treatment of idiopathic pulmonary fibrosis with etanercept: an exploratory, placebo-controlled trial. *Am J Respir Crit Care Med*. 2008;178(9):948–55.
- Demedts M, Behr J, Buhl R, Costabel U, Dekhuijzen R, Jansen HM, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med*. 2005;353(21):2229–42.
- King Jr TE, Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2008;177(1):75–81.
- Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet*. 2011;377(9779):1760–9.
- Raghu G, Brown KK, Bradford WZ, Starko K, Noble PW, Schwartz DA, et al. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. *N Engl J Med*. 2004;350(2):125–33.
- Raghu G, Anstrom KJ, King Jr TE, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med*. 2012;366(21):1968–77.
- Ziesche R, Hofbauer E, Wittmann K, Petkov V, Block LH. A preliminary study of long-term treatment with interferon gamma-1b and low-dose prednisolone in patients with idiopathic pulmonary fibrosis. *N Engl J Med*. 1999;341(17):1264–9.
- King Jr TE, Albera C, Bradford WZ, Costabel U, Hormel P, Lancaster L, et al. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet*. 2009;374(9685):222–8.
- Honore I, Nunes H, Groussard O, Kambouchner M, Chambellan A, Aubier M, et al. Acute respiratory failure after interferon-gamma therapy of end-stage pulmonary fibrosis. *Am J Respir Crit Care Med*. 2003;167(7):953–7.
- Kalra S, Utz JP, Ryu JH. Interferon gamma-1b therapy for advanced idiopathic pulmonary fibrosis. *Mayo Clin Proc*. 2003;78(9):1082–7.
- Jaffe HA, Buhl R, Mastrangeli A, Holroyd KJ, Saltini C, Czerski D, et al. Organ specific cytokine therapy. Local activation of mononuclear phagocytes by delivery of an aerosol of recombinant interferon-gamma to the human lung. *J Clin Invest*. 1991;88(1):297–302.
- Luppi F, Losi M, D'Amico R, Fabbri LM, Richeldi L. Endogenous blood maximal interferon-gamma production may predict response to interferon-gamma 1beta treatment in patients with idiopathic pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2009;26(1):64–8.
- Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002;346(12):896–903.
- Galie N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation*. 2008;117(23):3010–9.
- Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med*. 2010;363(7):620–8.
- Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2005;171(9):1040–7.
- Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, et al. Pirfenidone in idiopathic pulmonary fibrosis. *Eur Respir J*. 2010;35(4):821–9.
- Spagnolo P, Del Giovane C, Luppi F, Cerri S, Balduzzi S, Walters EH, et al. Non-steroid agents for idiopathic pulmonary fibrosis. *Cochrane Database Syst Rev*. 2010(9):CD003134.
- Walter N, Collard HR, King Jr TE. Current perspectives on the treatment of idiopathic pulmonary fibrosis. *Proc Am Thorac Soc*. 2006;3(4):330–8.

36. Kubo H, Nakayama K, Yanai M, Suzuki T, Yamaya M, Watanabe M, et al. Anticoagulant therapy for idiopathic pulmonary fibrosis. *Chest*. 2005;128(3):1475–82.
37. Noth I, Anstrom KJ, Calvert SB, de Andrade J, Flaherty KR, Glazer C, et al. A Placebo-Controlled Randomized Trial of Warfarin in Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med*. 2012;186(1):88–95.
38. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. *Am J Respir Crit Care Med*. 2011;184(12):1382–9.
39. Richeldi L, Ryerson CJ, Lee JS, Wolters PJ, Koth LL, Ley B, et al. Relative versus absolute change in forced vital capacity in idiopathic pulmonary fibrosis. *Thorax*. 2012;67(5):407–11.
40. Zappala CJ, Latsi PI, Nicholson AG, Colby TV, Cramer D, Renzoni EA, et al. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. *Eur Respir J*. 2010;35(4):830–6.
41. du Bois RM, Nathan SD, Richeldi L, Schwarz MI, Noble PW. Idiopathic Pulmonary Fibrosis: Lung Function is a Clinically Meaningful Endpoint for Phase 3 Trials. *Am J Respir Crit Care Med*. 2012 Jul 12. (Epub ahead of print)
42. Raghu G, Collard HR, Anstrom KJ, Flaherty KR, Fleming TR, King Jr TE, et al. Idiopathic pulmonary fibrosis: clinically meaningful primary endpoints in phase 3 clinical trials. *Am J Respir Crit Care Med*. 2012;185(10):1044–8.