Repeat bronchoalveolar lavage in idiopathic pulmonary fibrosis: proceed with caution?

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Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial lung disease with a median life expectancy of 3–5 years [1]. In recent years, management of IPF has been transformed with the worldwide approval of two anti-fibrotic therapies. In parallel, advances in the understanding of IPF pathogenesis have identified numerous targets for potential therapeutic intervention [2]. However, the adoption of anti-fibrotic therapies as the standard of care for patients with IPF has further increased the complexity of investigating novel therapeutics in clinical trials. New, innovative clinical trial design approaches are therefore being implemented. This includes early-phase trials designed not only to inform about drug dosing, safety and tolerability, but also to provide sufficient confidence on target engagement or potential efficacy to support progression to the much more costly later-phase studies.

In this issue of the *European Respiratory Journal*, Hirani *et al.* [3] report the findings of the first inhaled therapeutic to be investigated in a clinical study in patients with IPF. In a randomised, double-blind, multicentre, placebo-controlled phase I/IIa study they investigated the safety, tolerability and pharmacokinetics of TD139, an inhaled dry powder galectin-3 inhibitor. Galectin-3 is a cytokine that is upregulated in the bronchoalveolar lavage (BAL) fluid and serum of patients with IPF. It is believed to be a pleiotropic regulator of lung fibrosis through its ability to cross-link and promote signalling *via* multiple surface receptors, with previous studies reporting anti-fibrotic efficacy in murine models of lung fibrosis through inhibition of galectin-3-secreting macrophages [4, 5].

The study is notable as the first to describe an inhaled drug in patients with IPF, identifying a concentration in the lung >500-fold higher than in the blood, whilst providing biologic proof-of-concept that it achieves target engagement in the alveolar space associated with plasma changes in pro-fibrotic mediators. In the first part of the study, cohorts of 36 healthy subjects were evaluated with a range of doses of TD139, whilst in the second part of the study 24 patients with a multidisciplinary team diagnosis of IPF received TD139 or placebo for 14 days, with bronchoscopy with BAL performed on day 1 and day 14. Inhaled administration resulted in measurable, dose-dependent levels of the drug in plasma, epithelial lining fluid and alveolar macrophages, with suppression of galectin-3 expression on BAL macrophages as well as a decrease in plasma biomarkers associated with IPF progression. Together these findings have

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supported progression to a currently ongoing phase IIb study with TD139 in IPF (GALACTIC-1, NCT03832946).

TD139 was considered safe and tolerable in the cohort studied. In healthy subjects the most commonly occurring treatment-emergent adverse event was mild dysgeusia (distortion of sense of taste). However, the one post-treatment severe adverse event was a fatal episode of acute exacerbation of IPF (AE-IPF) in the TD139 IPF group, with new respiratory symptoms developing 2 days after the second BAL. AE-IPF has been defined by an expert International Working Group as an acute, clinically significant respiratory deterioration characterised by evidence of new, widespread alveolar abnormalities on computed tomography (CT) imaging [6]. It is well known that AE-IPF can occur unpredictably and at any point in the disease course. Whilst AE-IPF is more common in patients with physiologically and functionally advanced disease [6], the mean forced vital capacity of the sub-cohort which included this patient was 98% predicted, suggesting this patient did not have physiologically advanced disease. The study investigators acknowledged that the AE-IPF was possibly related to the second BAL at day 14 but considered it unrelated to the study drug TD139. Given this observation, even if only reported for one individual, some consideration is warranted into the safety of repeat BAL in patients with IPF.

Since the first conception of the flexible bronchoscope in the 1960s [7, 8], BAL has been considered a safe procedure and has been widely adopted as a means to sample the cellular and acellular components of distal bronchioles and gas exchange units [9, 10]. BAL is an invaluable research tool for disease pathogenesis studies, whilst in clinical practice it is used to inform the diagnosis and management of patients with lung diseases. The diagnostic role of BAL has been highlighted in recently published guidelines for hypersensitivity pneumonitis (HP), which suggest bronchoscopy and cellular analysis of BAL in patients with newly identified interstitial lung disease for whom the differential diagnosis includes fibrotic HP [11].

BAL is less commonly performed in patients undergoing investigation for IPF, although IPF guidelines provide a conditional recommendation to perform BAL in cases of newly diagnosed interstitial lung disease of uncertain cause where the CT pattern is not one of definite usual interstitial pneumonia [12]. Whilst BAL is considered a safe procedure, there are a small number of historical retrospective reports that it may increase the risk of acute respiratory deterioration in patients with IPF [13–16]. Possible mechanisms in susceptible individuals include the spreading of subclinical infection or saline lavage itself causing lung injury with loss of surfactant, thereby reducing surface tension and causing alveolar collapse [16]. To date no study has prospectively investigated BAL safety in patients with IPF, although recent analysis of the large PROFILE longitudinal cohort study identified research bronchoscopy to be a safe and well tolerated procedure in individuals with IPF [17]. In the 30 days following BAL, out of 223 patients who underwent bronchoscopy, six patients (2.7%) reported complications, with three treated with antibiotics for presumed lower respiratory tract infection; comparing the outcomes of patients who underwent bronchoscopy with those who did not, no difference in mortality up to 90 days was identified.

Consistent with BAL being a safe procedure, studies in healthy volunteers have identified evidence only of transient systemic and alveolar inflammation following BAL, with neutrophil recruitment and inflammatory cytokine elevation which had resolved by 72 h [18, 19]. However, given the biological dysfunction of the lung in IPF and recognised increased susceptibility to external insults, it is certainly plausible to speculate that in patients with IPF, bronchoscopy and BAL might prime the lung to an aberrant response in particular if bronchoscopy and BAL are repeated.

Repeat BAL in patients with IPF is rarely performed as part of standard of care and so available clinical safety data are limited. There are some historical reports that repeat bronchoscopy may be associated with increased risk of AE-IPF, although changes in disease classification and standards of care over time limit potential extrapolation to current practice. In the first description of AE-IPF following BAL in 1994, Hiwatari *et al.* [13] reported that out of 124 patients with IPF undergoing BAL, three patients (2.4%) subsequently developed an acute exacerbation and died of progressive respiratory failure. The three patients had undergone bronchoscopy with BAL and transbronchial lung biopsy between 1 and 7 months prior. In 2012 Sakamoto *et al.* [16] reported on the frequency of AE-IPF within 1 month of 201 BAL procedures performed in 111 patients. While none of 111 initial BAL procedures were followed by AE-IPF, there were four subsequent procedures followed by the onset of AE-IPF, with the relative risk of developing AE after second or later BAL procedures estimated to be 9.1 (95% CI 2.8–26.9).

Importantly, these small retrospective studies do not prove causality. Although AE-IPF have been identified to occur more frequently in older patients with more advanced disease, they can occur at any point in the disease course, with AE-IPF rates of up to 14.2% per year reported in observational cohort studies of patients with IPF [6], and so although plausible it remains unproven that repeat BAL does increase the risk of AE-IPF.

In recent years, a number of early-phase clinical trial studies have undertaken repeat BAL in IPF subjects with no reports of procedure-related adverse events in 40 patients [20, 21]. In these trials, as in the study of TD139, repeat BAL has provided invaluable data to support further clinical development of novel compounds. Thus, repeat BAL is an attractive methodology for early-stage IPF clinical trials. However, given the theoretical risk and the limited data on the outcomes of repeated BAL in patients with IPF, careful deliberation is warranted when considering this approach, in particular in the context of research studies including patient selection and fully informed consent.

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References

1 Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. *Lancet* 2017; 389: 1941–1952.
2 Sato S, Yanagihara T, Kolb MRJ. Therapeutic targets and early stage clinical trials for pulmonary fibrosis. *Expert Opin Investig Drugs* 2019; 28: 19–28.
3 Hirani N, MacKinnon AC, Nicol L, *et al.* Target inhibition of galectin-3 by inhaled TD139 in patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2021; 57: 2002559.
4 Delaine T, Collins P, MacKinnon A, *et al.* Galectin-3-binding glycomimetics that strongly reduce bleomycin-induced lung fibrosis and modulate intracellular glycan recognition. *ChemBioChem* 2016; 17: 1759–1770.
5 MacKinnon AC, Gibbons MA, Farnworth SL, *et al.* Regulation of transforming growth factor- 1-driven lung fibrosis by galectin-3. *Am J Respir Crit Care Med* 2012; 185: 537–546.
6 Collard HR, Ryerson CJ, Corte TJ, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. *Am J Respir Crit Care Med* 2016; 194: 265–275.
7 Ikeda S, Yanai N, Ishikawa S. Flexible bronchofiberscope. *Keio J Med* 1968; 17: 1–16.
8 Ikeda S. Flexible bronchofiberscope. *Ann Otol Rhinol Laryngol* 1970; 79: 916–923.
9 Technical recommendations and guidelines for bronchoalveolar lavage (BAL). Report of the European Society of Pneumology Task Group. *Eur Respir J* 1989; 2: 561–585.
10 Clinical guidelines and indications for bronchoalveolar lavage (BAL). Report of the European Society of Pneumology Task Group on BAL. *Eur Respir J* 1990; 3: 937–976.
11 Raghu G, Remy-Jardin M, Ryerson CJ, *et al.* Diagnosis of hypersensitivity pneumonitis in adults. An official ATS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2020; 202: e36–e69.
12 Raghu G, Remy-Jardin M, Myers JL, *et al.* Diagnosis of idiopathic pulmonary fibrosis. An Official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018; 198: e44–e68.
13 Hiwatari N, Shimura S, Takishima T, *et al.* Bronchoalveolar lavage as a possible cause of acute exacerbation in idiopathic pulmonary fibrosis patients. *Tohoku J Exp Med* 1994; 174: 379–386.
14 Suga T, Sugiyama Y, Ohno S, *et al.* Two cases of IIP which developed acute exacerbation after bronchoalveolar lavage. *Nihon Kyobu Shikkan Gakkai Zasshi* 1994; 32: 174–178.
15 Kim DS, Park JH, Park BK, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. *Eur Respir J* 2006; 27: 143–150.
16 Sakamoto K, Taniguchi H, Kondoh Y, *et al.* Acute exacerbation of IPF following diagnostic bronchoalveolar lavage procedures. *Respir Med* 2012; 106: 436–442.
17 Molyneaux PL, Smith JJ, Saunders P, *et al.* BAL is safe and well tolerated in individuals with idiopathic pulmonary fibrosis: an analysis of the profile study. *Am J Respir Crit Care Med* 2021; 203: 136–139.
18 Essen Von SG, Robbins RA, Spurzem JR, *et al.* Bronchoscopy with bronchoalveolar lavage causes neutrophil recruitment to the lower respiratory tract. *Am Rev Respir Dis* 1991; 144: 848–854.
19 Terashima T, Amakawa K, Matsumaru A, *et al.* BAL induces an increase in peripheral blood neutrophils and cytokine levels in healthy volunteers and patients with pneumonia. *Chest* 2001; 119: 1724–1729.
20 Maher TM, van der Aar EM, Van de Steen O, *et al.* Safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomised placebo-controlled trial. *Lancet Respir Med* 2018; 6: 627–635.
21 Lukey PT, Harrison SA, Yang S, *et al.* A randomised, placebo-controlled study of omipalisib (PI3 K/mTOR) in idiopathic pulmonary fibrosis. *Eur Respir J* 2019; 53: 1801992.