Gastro-oesophageal reflux and idiopathic pulmonary fibrosis: in search of evidence

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We need evidence for anti-reflux therapy in IPF
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Gastro-oesophageal reflux (GOR) is a frequent comorbidity in many chronic respiratory conditions, particularly in idiopathic pulmonary fibrosis (IPF) [1]. However, the evidence that GOR contributes to the pathophysiology of IPF and that interventions aimed at controlling GOR may influence the evolution of lung fibrosis remains elusive. Despite that, the 2015 update of the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association clinical practice guidelines for IPF provides a conditional recommendation for antacid treatment as a possible treatment for IPF [2], albeit with very low confidence in estimates of effect because data on the efficacy of antacid therapy effect are limited. The same guidelines provide a conditional recommendation for pirfenidone and nintedanib treatment in patients with IPF based on the results of phase 3 randomised controlled trials [2].

There is ample epidemiological evidence for the increased prevalence of gastro-oesophageal reflux disease (GORD) in IPF and other fibrotic disorders, and Raghu and co-workers were among the first to demonstrate the epidemiological link between GOR and IPF [3]. Oesophageal pH monitoring has estimated the prevalence of distal GOR in IPF at 67–88% and proximal GOR at 30–71% [4]. A recent prospective evaluation of 40 consecutive patients with IPF and 40 consecutive patients with interstitial lung disease other than IPF (non-IPF patients) showed that IPF patients had significantly higher oesophageal acid exposure, and increased number of acid, weakly acidic and proximal reflux events compared to non-IPF patients and healthy volunteers [1]. The reasons for this high prevalence of GOR in IPF patients are probably multiple: shared risk factors (ageing, tobacco smoke), increased recoil of the fibrotic lung that could dilate the lower oesophageal sphincter, and high prevalence of hiatal hernia [5, 6].

The main question for patients with this relentless fibrotic disorder, however, is whether treatment of GOR in patients with IPF provides any benefit. Clinical and experimental data suggest that chronic repeated acid exposure to the lower airways and alveoli may contribute to the fibrotic process in the lung [7, 8]. Observational data suggest that occult aspiration may play a role in some cases of acute exacerbation of IPF [9]. Evidence obtained from asymmetrical fibrosis further support the contribution of GOR to disease progression [10]. These data support the hypothesis that treating GOR may influence IPF behaviour, and many mechanisms have been proposed to explain a potential benefit of GOR treatment in IPF [11].

However, evidence of efficacy of GOR treatment has yet to be made. A retrospective analysis of patients with IPF reported that GORD-related treatment, especially antacid therapy, was associated with less radiological fibrosis and was an independent predictor of increased survival time in IPF patients [4]. An additional study reported on the outcome of patients with IPF randomly assigned to placebo in three National Heart, Lung, and Blood Institute IPF Clinical Research Network-sponsored randomised controlled

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trials [12]. After adjusting for sex and pulmonary function, patients who received antacid therapy had significantly less deterioration of pulmonary function than those not being treated [12]. A third study gave conflicting results. This study evaluated the effect of antacid therapy on disease progression in patients randomly assigned to placebo through analysis of three large, phase 3 trials of pirfenidone in IPF [13]. Antacid therapy did not improve outcomes in patients with IPF and might potentially be associated with an increased risk of infection in those with advanced disease (forced vital capacity (FVC) <70% predicted). In the two latter studies, antacid treatment was evaluated at trial baseline and a significant number of patients either initiated or discontinued antacid therapy during the trial. Moreover, both studies used prospectively collected data, but the study population was not randomised for antacid therapy or stratified for imbalances in comorbidities. It is quite clear that only prospective randomised controlled studies have the potential to answer definitively to the question of antacid therapy in IPF patients.

The problem is made even more complex due to the possible interaction between antacid therapy and antifibrotics (pirfenidone or nintedanib). For instance, some proton-pump inhibitors such as omeprazole, are moderate inducers of CYP1A2. Concomitant use with pirfenidone may theoretically result in a lowering of pirfenidone plasma levels [14]. Interestingly, a Japanese study suggested that antacid therapy improved the gastrointestinal tolerance of pirfenidone [15]. Concerning nintedanib, a *post hoc* analysis of the INPULSIS clinical trials showed that antacid medication did not influence the treatment effect of nintedanib in patients with IPF [16]. However, there was a greater risk of exacerbation in the patients receiving antacid medication at baseline and continued on placebo compared to the patients who did not receive antacid medication at baseline and continued on placebo [16].

Another level of complexity comes from the observation that antacid therapy is not sufficient to control acidic GOR in many patients and that antacid therapy does not control non-acid reflux and does not prevent microaspiration [17, 18]. Only anti-reflux surgery, which includes repair of hiatal hernia and fundoplication, usually through laparoscopy, has the potential to fully control GOR [19]. The feasibility of this surgical procedure has been evaluated in patients with severe lung function alterations [20, 21]. In a retrospective study, patients with IPF subjected to Nissen fundoplication demonstrated decreased oxygen supplementation needs during exercise and increased distance covered during 6-min walk tests [21].

In this edition of the *European Respiratory Journal*, Raghu *et al.* [22] report their unique experience on a series of IPF patients with worsening symptoms and pulmonary function, despite antacid therapy for abnormal GOR, and treatment with laparoscopic anti-reflux surgery (LARS). First, they report that the procedure was generally safe as there were no acute exacerbations of IPF in the post-operative period and no deaths in the 90-day period after LARS; the majority (81.5%) of patients were still alive 2 years after surgery. Secondly, the procedure effectively controlled GOR as the mean DeMeester score decreased from 42 to 4 ($p<0.01$). Thirdly, a trend toward FVC stabilisation was reported, although the rate of FVC decline pre- and post-LARS was not statistically different.

This study has clear limitations. First, it was uncontrolled, therefore it is difficult to determine the effect of the procedure on FVC decline on the basis of these data. Secondly, patients were highly selected, as evidenced by young age (mean age was 65 years) and relatively preserved lung function (FVC 72%). Most of the patients we see in daily clinical practice are older, and many of them have a more pronounced decrease in lung function, with comorbidities, and safety may be different in such a population. Thirdly, the patients were treated in a tertiary referral centre with a unique expertise in IPF and GOR management. Results might be different in less experienced centres. Fourth, the study included patients who were not receiving any antifibrotic drug, due to unavailability in the USA during the period the study recruited patients. Whether antifibrotic drugs may impact the safety and efficacy of LARS in IPF patients is unknown. LARS might interfere with stomach emptying and with pharmacokinetics of several drugs, including antifibrotic agents.

Now, the time has come to search for evidence. We need adequately powered controlled trials to determine whether GOR-targeted therapy, either surgical or medical, is useful for IPF patients. We remember a recent era when we were using steroids, immunosuppressants and N-acetylcysteine for IPF treatment [23]; then, phase 3 trials showed us that we were doing badly. We urgently need similar evidence for GOR treatment in IPF patients. The ongoing prospective and randomised phase 2 clinical study, "WRAP-IPF", will determine the safety and efficacy of LARS in IPF patients with abnormal acid GOR [24]. The results of this trial are eagerly awaited.

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