Anti-acid therapy in Idiopathic Pulmonary Fibrosis: to treat or not to treat?

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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, associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP) and with a median survival from the time of diagnosis of 2-3 years.[1] The exact pathogenesis of IPF is unclear, but probably involves recurrent injury to alveolar epithelial cells in genetically susceptible patients. Sources of potential injury include cigarette smoking, environmental pollutants, microbial agents and gastro-oesophageal reflux (GER).[1,2]

For the latter, already in 1976 Mays *et al.* hypothesized a relationship between reflux and pulmonary fibrosis.[3]

Since then, a well established strong association between gastro-oesophageal reflux disease (GERD) and IPF has been proven; the reported prevalence of GERD in patients with IPF ranges between 8% and 87%.[4,5] This large variation is probably due to differences in the methods used to determine GERD (pH-impedance, pH only or questionnaire) and the definitions of abnormal GER applied (for example, percentage of time pH <4 or DeMeester score).[6] Moreover, evidence obtained from asymmetrical fibrosis further support the contribution of GER to disease progression.[7]

The typical symptoms of heartburn are present in only 25-65% of patients with IPF and with confirmed pathological GERD from 24-h pH monitoring; therefore, the absence of symptoms does not preclude a diagnosis of GERD in this population.[6]

However, it is still unclear whether there is a causal relationship between IPF and GERD (i.e., whether GER increases risk of IPF or IPF increases risk of GER).[8] As a result, two long-standing hypotheses regarding the cause-effect relationship remain unresolved:

1) Chronic microaspiration causes recurrent injury to the bronchiolar and alveolar epithelium and drives the disease process in susceptible individuals to manifest IPF.
2) Decreased lung compliance of the fibrotic lung in patients with IPF (particularly in supine position/during sleep) causes increased swings in intrathoracic pressure and leads to dysfunctional lower esophageal sphincter, GERD, and microaspiration that perpetuate and/or accelerate the IPF disease process.[8]

The optimal diagnostic strategy to test for GERD in patients with IPF is uncertain. A comprehensive gastrointestinal history is mandatory. Barium swallow studies are generally unhelpful for diagnosing GERD in IPF, but might identify gross aspiration events or anatomical abnormalities such as hiatal hernia which is frequent in IPF patients.[6,9] Although 24-h pH monitoring and oesophageal manometry can identify GERD, guidance on when or whether to pursue these studies in IPF is lacking and the decision to proceed with these techniques should be individualised. However, 24-h pH monitoring will not identify non-acid reflux and all these studies are insensitive to microaspiration events.[6] Treatment of GERD includes conservative approaches (lifestyle modifications), pharmacological agents and surgical procedures.[6]

In the recently updated 2015 ATS/ERS/JRS/ALAT guidelines on treatment of IPF, anti-acid therapy has been given a conditional recommendation for use.[10] This recommendation, which is unchanged from the 2011 guideline document, is based on observational and retrospective studies and post-hoc analysis of patients randomly assigned to placebo in clinical trials of pharmacological interventions, the results of which suggested that patients given anti-acid therapy had slower disease progression as assessed by decrease in forced vital capacity (FVC), and improved survival compared with patients not receiving anti-acid therapy.[11,12]

Kreuter and colleagues, have attempted to further address the role of anti-acid therapy in patients with IPF by analyzing pooled data from the placebo groups of three studies of pirfenidone (CAPACITY 004, CAPACITY 006, and ASCEND).[13] These studies included 624 patients with equivalent numbers of patients on and off anti-acid therapy at study entry. The analyses did not show any benefit of anti-acid therapy on multiple outcomes measures, including a composite endpoint representing disease progression, change in FVC, and mortality, but instead showed that infections among the GERD-therapy group appeared to increase with increasing disease severity.[13] It is noteworthy that the number of patients included far exceeds the total number in the two prior manuscripts that suggested efficacy of antacid therapy.[11,12] Moreover, the pooled data from the two INPULSIS (nintedanib) trials showed that there was a greater decline in FVC in the patients receiving anti-acid medication [proton pump inhibitors (PPIs) or H2 receptor antagonists (H2RA)] at baseline and continued on placebo-for-nintedanib compared with the patients who received anti-acid medication at baseline and continued on nintedanib.[14]

The recent *post hoc* study by Kreuter and colleagues beyond its inherent limitation of a pooled *post-hoc* analysis, carries a number of restrictions, such as patients with advanced disease and those listed for lung transplantation (ie, FVC <50%), who could potentially benefit the most from anti-acid therapy, were not included, the observation time was limited to 52 weeks, some patients initiated or discontinued anti-acid therapy during the trial after their baseline assessment, patients on "anti-acid therapy" in this study were not exclusively on PPIs, it is not known whether or not the anti-acid therapy adequately treated GER, and what the potential role of non-acid reflux might be. These data also do not inform on the potential role of more definitive treatment options, specifically Nissen fundoplication.[15] Moreover, there were no pre-specified criteria that defined infection or respiratory infection, nor were the presumed episodes of infection adjudicated; thus, the site investigator's reported episodes of infection were subjective and arbitrary and the intensity, frequency, and extent of abnormal GER are unknown because these were not assessed. Also, the dose, duration, and specific anti-acid taken throughout the study period is unknown or not controlled as whether patients were taking the anti-acid treatment on a daily or as needed basis for symptomatic GER or simply taking the medication for assumed silent GER or for IPF; whether patients were taking the same dose and the same anti-acids captured in case report forms at baseline and throughout the trial period; whether patients were adhering to conservative measures to decrease the risks for aspiration, and finally if patients would silently have persistent abnormal acid GER is also unknown.[15]

In another study, Lee and colleagues reported beneficial effects in patients treated with anti-acids based on planned data analyses defined a priori; By contrast, in the *post-hoc* analysis by Kreuter and colleagues, the pooled population of patients with IPF enrolled in the pirfenidone trials were based on data noted in case report forms that was not intended to capture data for the diagnosis of GERD or the specifics of anti-acid treatment at baseline or during study period.[11,13]

The problem is even more complex due to the possible interaction between anti-acid therapy and antifibrotics (pirfenidone or nintedanib). For instance, some PPIs such as omeprazole, are moderate inducers of CYP1A2. Concomitant use with pirfenidone may theoretically result in a lowering of pirfenidone plasma levels.[16] Another level of complexity comes from the observation that anti-acid therapy is not sufficient to control acidic GER in many

patients and that anti-acid therapy does not control non-acid reflux and does not prevent microaspiration.[17] Only anti-reflux surgery, which includes repair of hiatal hernia and fundoplication, usually through laparoscopy, has the potential to fully control GER.[18]

It is important to recognize that there are several non fatal side effects associated with intermittent and/or prolonged use of PPIs, including rash, fatigue, diarrhea, headache, acid rebound after discontinuation, increase in non-acid reflux events, risk of osteoporosis, and increased risk of community-acquired pneumonia, dementia and major adverse cardiovascular events.[6] Another possible adverse effect of PPIs is on the homeostasis of the gastric microbiome and risk of microbial infection. This concern was partially alleviated by a recent meta-analysis of an observational study that found no statistically significant increase in the risk of hospitalization for community-acquired pneumonia among PPI users.[6] In contrast, studies have found association between increased abundance of specific bacterial sequences or bacterial loads and IPF disease progression, including the rate of lung volume decline.[19,20]

From the other side, there is also some evidence that anti-acid therapy may play a beneficial role in IPF despite their inability in controlling the gastric reflux per se or microaspiration. The alternate and biologically plausible mechanism(s) that may underlie the beneficial effect of PPIs in IPF may include downregulation of fibroinflammatory molecules, up-regulation of cytoprotective mechanisms, inhibition of fibroblast proliferation, and suppression of gastric acidity.[8,21]

In light of these findings, only well-designed randomised clinical trials (RCT) can answer the specific questions regarding the safety and efficacy of anti-acid therapy in patients with IPF, as "stand-alone"or "add-on" to current and/or other new antifibrotic therapies.[8,22,23] A first step is represented by two RCT, the Pilot Trial Of Omeprazole in Idiopathic Pulmonary Fibrosis (IPF) (PPIPF; NCT02085018) and that investigated the Treatment of IPF With Laparoscopic Anti-Reflux Surgery (WRAP-IPF; NCT01982968).[24,25]

COMPETING INTERESTS

All the authors declare that they do not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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