MINIREVIEW

Antacid therapy and disease outcomes in idiopathic pulmonary fibrosis: flip side of the story

Yohannes T Ghebre

Department of Radiation Oncology, Baylor College of Medicine, Houston, Texas 77030, USA

Correspondence: Yohannes T Ghebre
E-mail: yohannes.ghebre@bcm.edu
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It is well appreciated that majority of idiopathic pulmonary fibrosis (IPF) patients have gastric disorders including gastroesophageal reflux disease (GERD), dyspepsia and gastritis [1]. Accordingly, IPF patients are often prescribed antacid therapy such as histamine H2-receptor antagonists (H2RA) and proton pump inhibitors (PPIs). Occasionally, patients who repeatedly failed these medical interventions are referred to undergo surgical procedures to repair a segment of the esophagus and reinforce the closing function of the lower esophageal sphincter (LES). The later intervention is often more durable and effective in preventing the reflux of gastric juice and possible aspiration into the respiratory system [2]. However, despite limitations of the medical interventions, the use of H2RA and PPIs in IPF is still very common. Accordingly, a number of clinical studies have anecdotally and retrospectively assessed the safety and efficacy of antacid therapy in IPF.

In the past, several studies have reported beneficial effect of antacids in IPF disease outcomes including lower loss in pulmonary function, prolonged median survival and fewer episodes of acute exacerbations [3-6]. By contrast, a recent study by Kreuter *et al.* [7] published in *Lancet Respiratory Medicine* analyzed data pooled from three large clinical trials (CAPACITY 004, 006 and ASCEND) that primarily evaluated the safety and efficacy of pirfenidone and reported no benefit and a possible harm associated with the use of antacid therapy in IPF. This report was illuminated by a commentary from Nathan [8].

The two reports appear to be highly polarized and dismissive of the recent evidence-based guidelines for the treatment of IPF that conditionally recommended the use of antacid therapy in IPF [9]. However, it is important to highlight some important insights before overdrawing conclusions and making any changes to the recommendations by the Thoracic Societies: 1) why was only the data from patients in the *placebo arm* of the pirfenidone study presented in the publication? 2) would it not make more sense to have also analyzed and concurrently reported data from patients who were taking pirfenidone in the absence or presence of antacids? 3) were there findings in the study that appear to be downplayed or exaggerated? 4) what does the data (pertaining to question 2 above) that was not

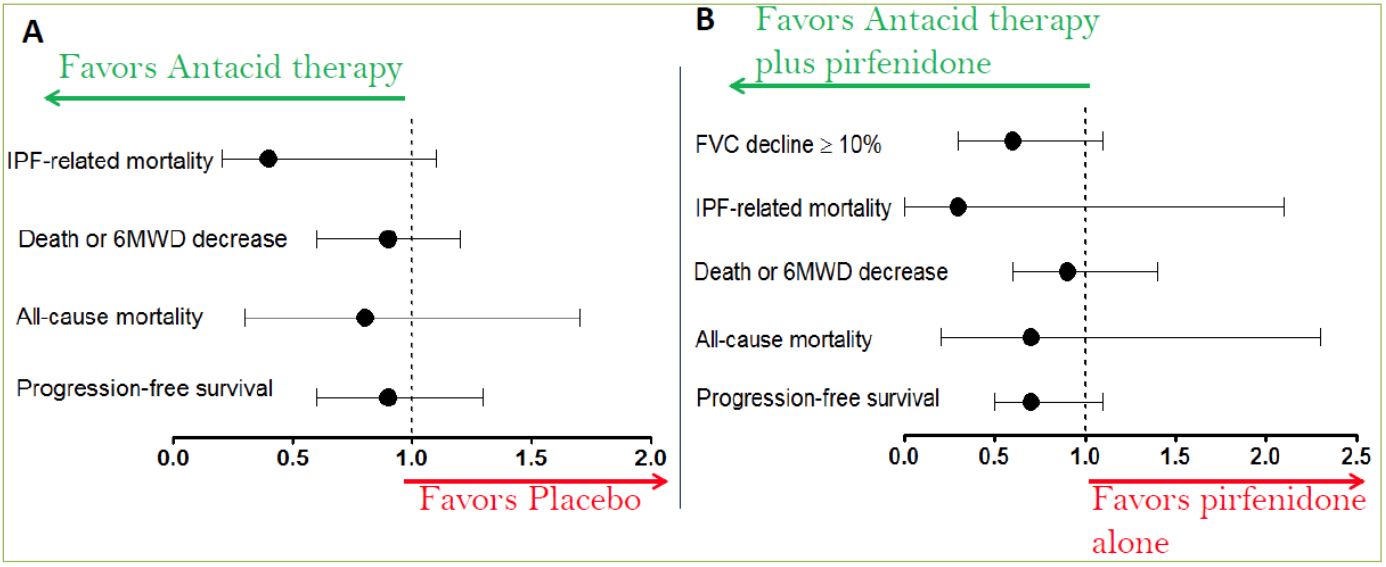

Figure 1. Odds ratio of adjusted data showing the effect of antacid therapy at 1-year when: A) compared with placebo or B) combined with pirfenidone. Odds ratio (median value) and 95% CI is shown in both dataset. Dataset A is drawn from Table 5 of Kreuter et al[7] and Dataset B is re-drawn from data presented by Kreuter et al ATS 2016[10].

reported look like? 5) how did the declared conflict of interest of the authors, including personal fees and grants influence partiality? 6) why was it absolutely necessary for one of the makers of a drug marketed for IPF to closely supervise the analysis and reporting of the study including paying for a ghost writer? 7) did the study provide enough evidence to compel a change in the guidelines? 8) what are some of the key differences between this study and some of the previous studies that favored the use of antacid therapy? 9) does the use of antacid therapy or surgery provide any possible benefit (or harm) to IPF patients? 10) what is the way forward regarding the use of antacids in IPF?

As discussed by Kreuter *et al* [7], the study, like other retrospective studies, has inherent limitations including the influence of confounders such as comorbidities and co-prescriptions. However, the study by Kreuter has additionally been compromised by entering and exiting of uneven number of patients to and out of the antacid therapy group. This crossing over, unless handled properly, may enable the latecomers to antacid therapy to simply be classified as 'no antacid therapy group' and compete against these who were on antacid therapy at baseline. To complicate matters, there is no information regarding the continued use of antacid therapy by these who were taking the therapy at baseline. One is simply led to take these important variables at face value and hone into the interpretation of results and conclusion.

At best, it is difficult to draw any firm conclusion from the unadjusted dataset (presented in Table 3 and Table 4) they provided since the patients in the antacid group had significantly higher GER-related and cardiovascular morbidity at baseline. Unfortunately, Kreuter *et al* not only have relied on unadjusted data (Table 4) to report how significantly the use of antacid therapy increased the risk of infection but also made this statement to be the main finding of the study. This flawed and exaggerated conclusion requires caution by every clinician who treats IPF patients and especially those who are recent graduates and doctors-in-training. If at all, it was only a subset of the sickest IPF patients in the antacid group that experienced increased risk of infection. However, this cannot and should not be pinned to the use of antacid therapy as the set of data that led to this conclusion is not adjusted and as a result is likely to have been influenced by several unaccounted variables. Meanwhile, the biased conclusion and unfair interpretation of the unadjusted data has confounded some important findings in the *adjusted* part of their analysis (Table 5). This Table shows that the use of antacid therapy numerically *favored*, without reaching statistical significance: i) progression-free survival, ii) all-cause mortality, iii) death or 6 minute walk distance (6MWD) decrease by 10% or more, and iv) IPF-related mortality (p=0.077) (Figure 1A above). Unfortunately, the authors have largely ignored discussing any of these potentially favorable outcomes associated with the use of antacid therapy. In addition, citing "data not shown", they revealed that poor compliance with antacid therapy might be associated with increased mortality. However, this possibility was swiftly rejected by the authors.

Meanwhile, their finding that was not reported (for one reason or another) in this study but was presented at the

recent American Thoracic Society (ATS) meeting in San Francisco (Abstract A2689 and Poster 201) [10] is even more stimulating. This study analyzed data from patients who were in the *pirfenidone arm* (of the above three large clinical trials) in the presence or absence of antacid therapy. This study had 273 patients in the pirfenidone plus antacid group and 350 patients in the pirfenidone without antacid group. Their unadjusted data showed that the use of antacid therapy significantly reduced the decline in lung function by 10% or more (p=0.0273). Similarly, their adjusted data numerically favored the use of antacid therapy for: i) progression-free survival, ii) all-cause mortality, iii) death or 6MWD decrease by 10% or more and iv) IPF-related mortality (Figure 1B above). Intriguingly, this set of data has its own merits as it eludes to the possible benefit of combining the use of pirfenidone with antacid therapy. In particular, since it is most likely that any emerging drug for IPF has to be tested in combination with the standard of care (e.g. pirfenidone).

In addition, the significance in overall infections they reported in the *Lancet Respiratory Medicine* paper did not stay significant in the second (i.e. pirfenidone plus antacid) analysis. Now, since the authors and Nathan made so much ado about unadjusted data, would it not be appropriate to make similar claims about the significant or numerically trended benefits associated with the use of antacid therapy in IPF from these two studies? As Nathan wrote, there may not be a "commercial appetite" with testing and developing antacid therapy for IPF. However, if proven to be effective in prospective studies, a combination of pirfenidone with antacid therapy may actually reduce the hefty dose (over 2 grams a day) and cost (over 90,000/patient/year) of pirfenidone and make a treatment plan more affordable and accessible for IPF patients who deserve the best possible treatment at the lowest possible cost. Meanwhile, any possible increase in risk of respiratory infection associated with antacids or GERD may be managed on a case-by-case basis while allowing patients to possibly benefit from antacid therapy in their IPF-related disease outcomes. This is particularly appealing especially given the several other retrospective clinical studies that reported significant benefit associated with the use of antacid therapy in IPF.[4-6] However, such prospect may well be against the money making scheme of industry and for that reason alone, a prospective study evaluating the use of antacid therapy (e.g. PPIs) as stand-alone or add-on to the already approved drugs may never be pursued.

Conflicting interests

YTG is an inventor on patents, owned by Stanford University, that protect the use of agents, including the PPIs, for therapeutic use of new indications including IPF. YTG is a cofounder of Altitude Pharma, Inc.; a biotechnology company developing PPI-based therapy for IPF.

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Author contributions

Y.T.G. conceived the idea and wrote, revised and finalized the manuscript.

Abbreviations

ASCEND: Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis; ATS: American Thoracic Society; GERD: gastroesophageal reflux disease; H2RA: histamine-2 receptor antagonists; IPF: idiopathic pulmonary fibrosis; LES: lower esophageal sphincter; PPIs: proton pump inhibitors; 6MWD: six minute walk distance.

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