Randomized, double-blind, placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis

BACKGROUND:

• Idiopathic pulmonary fibrosis (IPF) is a chronic, fibrosing interstitial lung disease characterized by progressive dyspnea and cough. Chronic cough is a major and disabling symptom affecting up to 80% of patients with IPF, and a strong correlation has been demonstrated between objective cough frequency and health-related quality of life. Nevertheless, treatment of cough associated with IPF remains notoriously difficult and conventional antitussive treatments have limited therapeutic effect. Gastro-esophageal reflux disease (GERD) is more prevalent in patients with IPF compared with the general population and those with other chronic lung diseases and is thought to worsen cough. Many patients with IPF use antacids for relief, yet there are currently no large, randomized, controlled trials evaluating the efficacy of PPIs in relation to cough frequency in IPF, and assessing their safety.

OBJECTIVE:

• This pilot trial was designed to assess the feasibility of a randomized, controlled trial of omeprazole in IPF, with particular reference to safety and whether any potential effect on cough would emerge. Ultimately, the aim of the study was to determine whether a larger definitive multicenter trial is worthwhile.

METHODS

• Type of study design

A single-center, double-blind, placebo-controlled, randomized, parallel pilot trial

• Study duration

90 days

• Important inclusion/exclusion criteria

Inclusion:

- IPF considered to be most likely diagnosis
- History of cough with or without exertional dyspnea
- Age 40-85 years
- Patients taking a PPI during screening were potentially eligible.
- Patients taking short courses (e.g. 2 months) of PPI were considered eligible once the treatment had been discontinued for a minimum of 1 month.
- Patients taking antacids at the time of screening were eligible if they have been off these treatments for a period of at least 2 weeks.

Exclusion:

- Concomitant use of warfarin, diazepam, phenytoin or ketoconazole
- Concomitant use of a regular PPI, antacid, prokinetic or raft alginate during the trial period
- Respiratory infection or exacerbation of IPF in the 4 weeks before starting study drugs
- Active trial of treatment for IPF started in the 4 weeks before starting study drugs
- Pregnant or lactating

• Drug regimens/dosages used

Omeprazole 20mg orally BID or
Placebo orally BID

• Outcome measures (efficacy and safety)

Primary Outcome: The mean change in cough frequency defined as (total number of coughs/total recording time in hours) which was assessed using an ambulatory cough recorder at baseline and the end of treatment.

Secondary Outcomes:

- Change in participant-reported symptoms of cough using the validated Leicester Cough Questionnaire (LCQ).
- Change in participant-reported symptoms of reflux using the validated De Meester reflux-related symptoms questionnaire (DeMRQ), the Reflux Symptoms Index (RSI),the Gastrointestinal Quality of Life Index (GIQLI)
- Improvements in physical exams including pulmonary function tests (PFTs) and a 6-minute walk distance (6MWD)

• Data handling method used

Intent-to-treat

RESULTS

• Number of patients who completed study (total and in each treatment)

Total: 40
Omeprazole: 20
Placebo: 20

Primary outcome: There was a greater reduction in 24 hours cough frequency in the omeprazole group compared with placebo. At the end of the study, geometric mean was 4.6 per hour (95% CI 2.4 to 8.7) in the omeprazole group and 8.3 per hour (95% CI 5.3 to 12.9) in the placebo group. Geometric mean cough frequency at the end of treatment, adjusted for baseline, was 39.1% lower (95% CI 66.0% lower to 9.3% higher) in the omeprazole group compared with placebo. - analyzed using an analysis of covariance (ANCOVA) model, adjusted for baseline cough frequency.

Secondary Outcomes: Participant-reported symptoms of cough (using the LCQ) and reflux (using the DeMRQ, the GIQLI and the RSI) were assessed. Overall, there was no clinically meaningful difference for participant-reported outcome measures between baseline and end of treatment in either group. Functional status (assessed by PFTs and 6MWD) was obtained at baseline and end of treatment for each group. No clinically meaningful difference in PFTs or 6MWD values was observed between baseline and end of treatment for either group. - secondary clinical outcome measures were analyzed using similar ANCOVA models.

• Authors stated conclusions

On average, cough was reduced more in the omeprazole group compared to placebo. Although this wasn't significant due to power not being established as this study is a pilot trial, these findings warrant and support a large, randomized controlled clinical trial in the future.

STRENGTHS

- Randomized using blocks to avoid variation between the 2 treatment groups
- Used placebo as control
- First ever trial determining if omeprazole can help decrease cough in patients with IPF
- Intention-to-treat analysis

LIMITATIONS

• Patients with GERD could have been included in the study, however, there was not specific inclusion criteria that states patients must have a diagnosis of GERD. One of the secondary outcomes includes 3 different questionnaires for reflux symptoms even though some of the participants may not have had reflux symptoms associated with GERD. Type 2 error is possible as a 39.1% difference, although not statistically significant, is large enough to be due to treatment and not chance. Authors state that there is clinical significance, however, this cannot be clinically significant as the findings are not statistically significant. Authors conclusions are one-sided in favor of omeprazole. No power was established, small sample size recruited from 1 major center and 6 small clinics, and no effect size established prior to the results being reported. Timing of omeprazole prior to meals and lack of controlled diet, some secondary outcomes were subjective questionnaires vs. objective findings, adherence rates not established, and high rates of adverse events were present.

CONCLUSIONS

• In conclusion, the mean frequency of cough reduction from the end of the study adjusted for baseline was 39.1% lower in the omeprazole group when compared to placebo. This mean decrease in cough frequency was not significant, however, a Type 2 error may be present. While the percentage decrease was 39.1%, the actual result was a decrease of 8.3 coughs/hour at baseline to 4.6 coughs/hour after omeprazole use for 90 days. While the percentage change appears to be large, the actual change is a difference of 4 coughs/hour. It is difficult to determine if this change is clinically significant. Additionally, there was no cough or reflux relief from omeprazole compared to placebo at the end of the study based on validated participant-answered questionnaires.

• While the study had flaws, there is a need to find an efficacious product as cough and reflux are prominent in patients with IPF and no current treatment options exist.

• Further studies are needed to assess both safety and efficacy of omeprazole in patients with IPF.

Reference: Dutta P, Funston W, Mossop H, Ryan V, Jones R, Forbes R, Sen S, Pearson J, Griffin SM, Smith JA, Ward C, Forrest IA, Simpson AJ. Randomized, double-blind, placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis. Thorax. 2019 Apr;74(4):346-353.

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