



Efficacy of Esomeprazole for Treatment of Poorly Controlled Asthma

Gastroesophageal reflux and asthma, both of which are common conditions, often coexist in the same patient. Persons with asthma are particularly prone to asymptomatic gastroesophageal reflux. Esophageal pH-monitoring studies have shown that 32 to 84% of persons with asthma have abnormal acid reflux and about half of patients with asthma who have reflux have no symptoms. However, the role of gastroesophageal reflux in the development or persistence of asthma symptoms is not known. Symptoms of asthma - cough and chest discomfort - may overlap with those of gastroesophageal reflux, making it difficult to distinguish between the two conditions. Moreover, the causal relationship between asthma and gastroesophageal reflux is complex. Acid reflux causes bronchoconstriction through microaspiration into the airways, as well as through reflex-mediated effects of acid on the esophagus or upper airway. Conversely, asthma-related bronchoconstriction can induce acid reflux. Descent of the diaphragm with hyperinflation increases the pressure gradient between the abdomen and thorax and may cause the lower esophageal sphincter to herniate into the chest, where its barrier function is diminished. This process may be exacerbated by the accentuated negative inspiratory pleural pressure in acute asthma, which opposes the tone of the lower esophageal sphincter. Furthermore, beta-agonists and methylxanthine bronchodilators may decrease the tone of the lower esophageal sphincter, but it has been difficult to show that these agents actually worsen reflux.

Proton-pump inhibitors are effective in suppressing the production of gastric acid and reducing symptoms of gastroesophageal reflux, whether or not asthma is present. Previous trials have had conflicting results regarding the beneficial effects of treatment with proton-pump inhibitors in patients with asthma who have frequent symptoms of gastroesophageal reflux disease. Whether proton-pump inhibitors improve asthma control in patients with minimal or no symptoms of gastroesophageal reflux is unknown, and whether objective measurement of acid reflux can be used to tailor treatment with proton-pump inhibitors to individual patients has not been established. Current guidelines recommend that physicians consider evaluating patients who have poorly controlled asthma, especially those with nighttime symptoms, for gastroesophageal reflux disease, even in the absence of suggestive symptoms of the disease. If gastroesophageal reflux is present, treatment recommendations include the use of a proton-pump inhibitor. However, patients with asthma who are receiving treatment for gastroesophageal reflux incur substantially higher diagnostic and treatment costs than do patients with asthma of similar severity who are not receiving treatment for this diagnosis. We compared esomeprazole with placebo in patients with poorly controlled asthma. Our primary objective was to determine whether acid-suppression therapy would improve asthma symptoms. A secondary objective was to determine whether ambulatory esophageal pH monitoring would identify patients with minimal or no symptoms of gastroesophageal reflux who might have a response to treatment.

METHODS

Participant Selection

We conducted a randomized, placebo-controlled, double-blind trial of esomeprazole (Nexium, AstraZeneca) in patients who had asthma that was inadequately controlled despite therapy with moderate or high doses of inhaled corticosteroids. Inclusion criteria were an age of 18 years or older; a diagnosis of asthma by a physician, with the diagnosis supported by either a positive methacholine challenge test or documentation of a 12% increase in the forced expiratory volume in 1 second (FEV1) after use of a bronchodilator; at least 8 weeks of stable use of an inhaled corticosteroid at a dose equivalent to 400 µg of fluticasone per day or more; and poor asthma control as defined by either a score on the Juniper Asthma Control Questionnaire (JACQ) of 1.5 or higher (on a scale of 0 to 6, with lower scores indicating better control of symptoms and with 0.5 as the minimal clinically important difference between scores) or the occurrence of more than one acute episode of asthma requiring unscheduled medical care in the previous year. Participants were excluded if they had smoked cigarettes within the previous 6 months or had a history of 10 or more pack-years of smoking; had an FEV1 of less than 50% of their predicted

value³⁰; had undergone surgery for reflux or peptic ulcer; had clinical indications for acid-suppression treatment (i.e., two or more episodes per week of heartburn requiring antacids); had used antireflux medication within the previous month; or were taking drugs that could interact with proton-pump inhibitors, such as theophylline, iron supplements, warfarin, antifungal drugs, or digitalis. Participants were also excluded if they were pregnant, could not tolerate proton-pump inhibitors, or had any serious illness that would interfere with participation in the trial. The study was approved by the institutional review board at each participating center, and all participants provided written informed consent.

Study Design

The study was conducted at 19 clinical centers from October 2004 through early May 2008. Data were analyzed at the coordinating center at Johns Hopkins University. The study was designed as a two-group, parallel-design, randomized clinical trial to test the hypothesis that esomeprazole was superior to placebo in improving asthma control. Participants who met the eligibility criteria were enrolled in a 2- to 8-week run-in period during which time they completed baseline daily asthma diaries and underwent pH testing. Participants were randomly assigned in a 1:1 ratio to receive either 40 mg of esomeprazole twice daily or a similar-appearing placebo. Participants and study staff were unaware of the group assignments. The randomization schedule was stratified according to clinic site with the use of a permuted block design with concealed allocation. After randomization, participants returned to the clinic for assessments of outcome measures every 4 weeks for 24 weeks.

Outcome Measures

For the duration of the trial, participants maintained diaries to record morning peak expiratory flow, asthma symptoms, nocturnal awakening, and use of beta-agonists. The primary outcome measure was the rate of episodes of poor asthma control. Such episodes were defined by a decrease of 30% or more in the morning peak expiratory flow rate on 2 consecutive days, as compared with the patient's best rate during the run-in period; an urgent visit, defined as an unscheduled health care visit for asthma symptoms; or the need for a course of oral prednisone for treatment of asthma. Use of a beta-agonist was not included as a criterion in this definition because of the possibility that participants might use beta-agonists for treatment of symptoms related to gastroesophageal reflux. In a secondary analysis, we added to the above definition the use of beta-agonists for asthma symptoms (four or more inhalations in 1 day at a dose above the baseline dose). The outcome measure we used - episodes of poor asthma control - incorporates key measures that are clinically relevant and are responsive to therapy such as inhaled corticosteroids. Other asthma symptoms recorded in daily diaries were considered to be secondary outcomes.

Secondary outcomes recorded at each visit were the results of spirometry before and after inhalation of 180 µg of albuterol, the score on the JACQ, the score on the Asthma Symptom Utility Index, the score on the Mini Asthma Quality of Life Questionnaire (MiniAQLQ) and the score on the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36). Methacholine airway reactivity, expressed as the inhaled methacholine concentration causing a 20% reduction in FEV1 (PC₂₀), was measured at baseline and at 24 weeks in participants with an FEV1 that was 70% or more of their predicted value.

The presence or absence of esophageal reflux was ascertained with the use of ambulatory pH monitoring. Studies were reviewed for technical quality at a central reading center. To be considered technically satisfactory, a study had to have a total recording time of 16 hours or more and include at least one meal and 2 hours of monitoring while the patient was lying down. Reflux was considered to be present if the pH was less than 4.0 for more than 5.8% of the total time, more than 8.2% of the time the patient was upright, or more than 3.5% of the time the patient was lying down. Symptoms of gastroesophageal reflux were assessed with the use of the Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS)-Distress Version, which measures both the number and the severity of symptoms.

Study Oversight

The study was designed and supervised by the steering committee of the American Lung Association Asthma Clinical Research Centers, which approved the publication of the study. The data were collected at the clinical centers and were analyzed at the data coordinating center (see Appendix). The writing committee wrote the manuscript and takes full responsibility for the accuracy and completeness of the article.

Esomeprazole and matching placebo were donated by AstraZeneca, but AstraZeneca had no role in the design or conduct of the study or in the analysis or interpretation of the data. The American Lung Association Asthma Clinical Research Centers are not bound by any confidentiality agreement with respect to the study results.

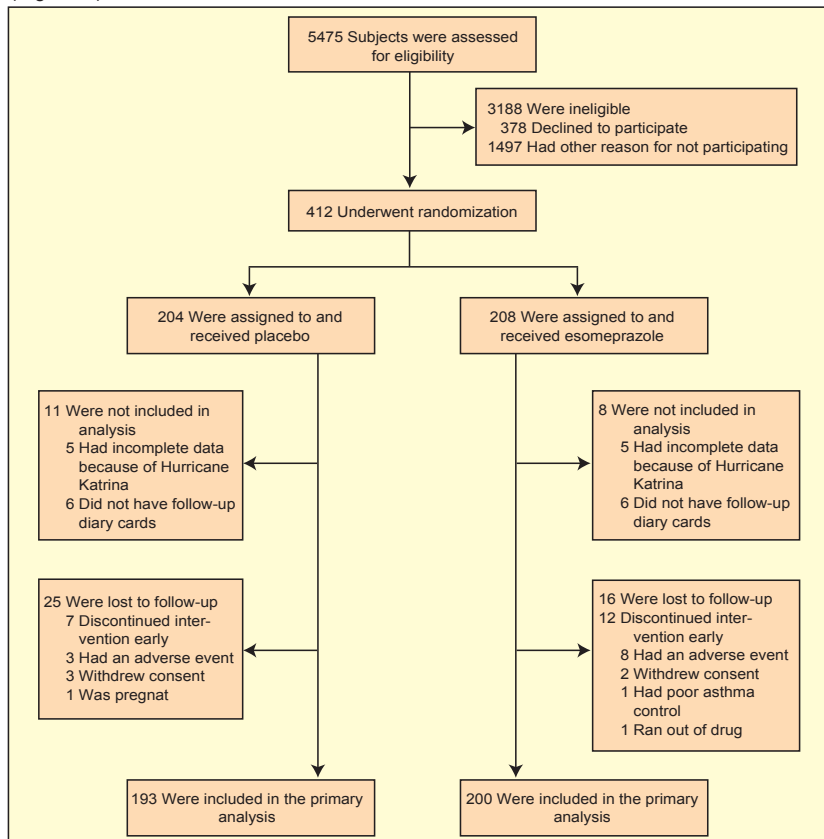
Statistical Analysis

We calculated that with a sample size of 400 participants, the study would have 77 to 97% power, with a two-sided type I error rate of 5% and 10% loss of data, to show a relative difference of 33% in the proportion of participants having one or more episodes of poor asthma control, assuming a rate of 40 to 60% in the control group. The primary outcome was the rate of episodes of poor asthma control; by basing the power calculation on the proportion of participants in each group who had one or more events, rather than on the event rate, we obtained a conservative estimate of power. All analyses were performed according to treatment assignment, and all available data were included in the evaluations, regardless of whether or not they discontinued the assigned treatment (modified intention-to-treat analysis).

RESULTS

Characteristics of the Participants

A total of 412 patients were randomly assigned to one of the two groups in the study (Figure 1)



Enrollment, Randomization and Follow-up of Study Participants.). Because of Hurricane Katrina, data from 10 patients in New Orleans were incomplete and were not included in the analysis. The majority of the patients were women, and most had lung function that was at the low end of the normal range and very poor asthma control, as evidenced by a mean JACQ score of 1.9. Approximately 15% of the participants reported that they had a history of gastroesophageal reflux, but the mean symptom scores were low. Gastroesophageal reflux, as assessed by ambulatory pH monitoring, was present in 41% of the patients in the placebo group and 40% of the patients in the esomeprazole group. The asthma characteristics were similar in the two study groups (Table 1 TABLE 1 Baseline Characteristics of the Study Participants. Baseline Characteristics of the Study Participants.).

When we defined an adherent participant as one who took both doses of the drug or placebo on at least 80% of the days during the study period, the rate of adherence in the placebo group was similar to the rate in the esomeprazole group, as assessed by diary cards (86% and 84%, respectively; P=0.53) and as assessed by pill counts (82% in each group, P=0.91). Ninety-four percent of the participants in the placebo group and 91% of the participants in the esomeprazole group took one or more doses of the study drug on at least 80% of the days (P=0.21). Esomeprazole was generally very well tolerated, but a few more participants in the esomeprazole group than in the placebo group discontinued treatment because of adverse effects (nine vs. three participants).

Few serious adverse events were reported in either the esomeprazole group or the placebo group (11 and 17 events, respectively, P=0.25); three hospitalizations for asthma exacerbations were reported in the esomeprazole group and four in the

Table 1. Baseline Characteristics of the Study Participants.*

Characteristic	Placebo (N=199)	Esomeprazole (N=203)
Age at randomization - yr	42 ± 13	42 ± 13
Male sex - %	28	36
Race or ethnic group - %†		
White	52	50
Hispanic	9	9
Other	3	2
Former smoker - %	20	15
Body-mass index‡		
Mean	32 ± 8	32 ± 9
≥30 - %	54	50
Age at onset of asthma - yr	17 ± 17	17 ± 16
Use of inhaled short-acting beta-agonist for asthma ≥2 times/wk - %	83	79
Unscheduled health care visit for asthma in previous year - %	63	54
Use of corticosteroids for asthma - %		
Oral corticosteroids in previous year	52	48
Inhaled corticosteroids		
Daily use	100	100
Combination of fluticasone and salmeterol	75	79
Asthma scores§		
JACQ	1.9 ± 0.8	1.8 ± 1.08
ASUI	0.74 ± 0.18	0.76 ± 0.15
MiniAQLQ	4.7 ± 1.2	4.7 ± 1.2
SF 36 quality-of-life score¶		
Physical component	42 ± 10	43 ± 10
Mental component	49 ± 10	50 ± 11
Pulmonary function		
No. of participants with measurement	198	203
FEV ₁		
Prebronchodilator - of predicted value	78 ± 15	76 ± 16
Postbronchodilator - % increase from prebronchodilator value	10 ± 10	11 ± 16
FVC		
Prebronchodilator - % of predicted value	87 ± 16	87 ± 14
Postbronchodilator - % increase from prebronchodilator value	5 ± 8	6 ± 11
FEV ₂₀		
No. of participants with measurement	92	8
PC ₂₀ contraindicated - no./total no. (%)	102/198 (52)	117/202 (58)
pH monitoring		
No. of participants with data	151	153
Positive result - %	41	40
GSAS**		
No. of participants assessed	199	203
No. of symptoms	7 ± 3	6 ± 4
Distress score	0.60 ± 0.46	0.51 ± 0.47
Conditions other than asthma - %††		
No. of participants with data	199	203
Gastroesophageal reflux disease	19	10
Eczema	20	10
Sinusitis	43	34
Rhinitis	61	58
Food allergies	24	15
Allergies that worsen asthma	78	78

* Plus-minus value are means ±SD. MiniAQLA denotes Mini Asthma Quality of Life Questionnaire, ASUI Asthma Symptom Utility Index, FEV₁ forced expiratory volume in 1 second, FVC forced vital capacity, GSAS Gastroesophageal Reflux Disease Symptom Assessment Scale, JACQ Juniper Asthma Control Questionnaire, PC₂₀ the concentration of inhaled methacholine causing a 20% reduction in FEV₁, and SF-36 Medical Outcomes study 36-Item Short-Form General Health Survey.
 † Race or ethnic group was self-reported.
 ‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
 § Scores on the JACQ range from 0 to 6, with lower scores indicating better asthma control and 0.5 as the minimal clinically important difference; scores on the ASUI range from 0 to 1, with higher scores indicating less severe asthma; scores on the MiniAQLQ range from 1 to 7, with higher scores indicating better quality of life and 0.5 as the minimal clinically important difference.
 ¶ Scores on the SF-36 range from 1 to 100, with higher scores indicating better quality of life and 5 as the minimal clinically important difference.
 | Predicted values for FEV₁ and FVC are from Hankinson et al.³⁰
 ** The number of symptoms on the GSAS ranges from 0 to 15. The distress score ranges from 9 to 3, with lower numbers indicating less distress.
 †† These conditions were self-reported.

placebo group. One patient in the esomeprazole group died after surgery for a bronchial carcinoid that was discovered during the study.

Episodes of Poor Asthma Control

Overall, the participants had persistent, poorly controlled symptoms of asthma. Approximately 42% of the participants had an episode of poor asthma control according to the definition that did not include the use of beta-agonists as a criterion, and 61% had an episode according to the definition that included the increased use of beta-agonists. Over the course of the 24 weeks of follow-up, about 18% of the patients required an urgent care visit or a course of prednisone. The annualized rates of episodes of poor asthma control and of the individual components (a fall in the peak expiratory flow rate, an urgent care visit, a course of corticosteroids, and increased use of beta-agonists) did not differ significantly between the treatment and placebo groups. Night awakening due to asthma occurred on one or more occasions in about half of the participants and the rate did not differ significantly between the two group.

Secondary Outcomes

Pulmonary function as measured by spirometry, bronchodilator response, peak expiratory flow rate, and airway reactivity did not change during the study and did not differ significantly between the two groups. Asthma symptoms, asthma control and quality of life, as assessed by questionnaires, all improved slightly during the trial but did not differ significantly according to the group assignment. Gastroesophageal-reflux-symptom scores, which were, by design, low at baseline, showed small improvements during the study, but did not differ significantly according to the group assignment.

Subgroup Analyses

We performed prespecified subgroup analyses to determine whether we could identify a subgroup that was likely to benefit from esomeprazole therapy. For all outcomes, there was no significant interaction between abnormal gastroesophageal reflux, as assessed by pH monitoring, and the group assignment, indicating that patients with documented gastroesophageal reflux did not have a response to treatment with proton-pump inhibitors that differed from the response of patients without documented reflux. Neither the body-mass index nor the presence or absence of night awakening identified a group of patients who had a response to proton-pump inhibitors. In addition, there was no interaction of treatment effect with age; race or ethnic group; sex; obesity; former smoking status; asthma control or severity scores; use of long-acting beta-agonists; self-reported sinusitis, rhinitis, or gastroesophageal reflux; or the GSAS distress score.

Discussion

The purpose of this trial was to determine whether the use of a proton-pump inhibitor, esomeprazole, in doses large enough to suppress gastric acid, would improve asthma control in patients with inadequately controlled asthma who did not have frequent symptoms of gastroesophageal reflux. We used a dose of esomeprazole that was higher than that typically used to treat symptomatic gastroesophageal reflux in order to increase our confidence that there was adequate suppression of gastric acid. Moreover, we performed ambulatory esophageal pH-monitoring studies to establish whether persons with documented acid reflux might benefit more from therapy with a proton-pump inhibitor than persons without documented acid reflux. After following 402 patients for 6 months, we were not able to show any treatment benefit with respect to the primary outcome - the rate of episodes of poor asthma control - or with respect to secondary outcomes, including asthma symptoms, nocturnal awakening, quality of life and lung function. Moreover, there was no significant difference in asthma-related outcomes between patients in whom reflux was documented and those in whom it was not.

A systematic review of 12 small trials concluded that, although most of the studies showed that asthma-related outcomes were better when the patients were treated with proton-pump inhibitors, some of the studies had design flaws and the studies did not show consistent improvement in the same asthma outcomes. More recently, Littner and colleagues reported the results of a 6-month placebo-controlled trial involving 207 patients with moderate-to-severe asthma and definite symptoms of gastroesophageal reflux. Treatment with 30 mg of lansoprazole twice daily did not improve the primary outcome of daily asthma symptoms, but it did result in a reduction in exacerbations and an improvement in asthma-related quality of life. The reduction in exacerbations was greatest among patients taking more than one class of medication for control of asthma. Kiljander and colleagues conducted a three-strata, 24-week, multicenter, international trial involving patients with asthma who had nocturnal asthma symptoms, symptoms of gastroesophageal reflux, or both, and who were treated with 40 mg of

esomeprazole twice daily. Overall, there was no efficacy in terms of daily peak expiratory flow rate, exacerbations, or asthma symptoms. However, in the stratum of 350 patients who had both symptoms of gastroesophageal reflux and nocturnal asthma symptoms, the peak expiratory flow rate improved, but there was no benefit with respect to FEV1, rescue-inhaler use, symptom scores, or nocturnal awakening. The esomeprazole-related improvement was most pronounced among patients who were taking long-acting beta-agonists.

This study differs from previous trials in that we excluded patients who had symptoms of gastroesophageal reflux two or more times per week. Our rationale was that these patients already have an indication for acid-suppression treatment, irrespective of their asthma. In our study population, we found no benefit from proton-pump inhibitors with respect to any primary or secondary asthma-related outcome measure. Moreover, ambulatory pH-monitoring studies did not identify a subgroup that was likely to benefit from therapy with proton-pump inhibitors. We also did not find that patients taking long-acting beta-agonists were more likely to have a response to proton-pump inhibitors. Therefore, taken as a whole, the weight of evidence indicates that proton-pump inhibitors should not be routinely prescribed for asthma symptoms if the patient does not have symptoms of gastroesophageal reflux. It should be noted, however, that this trial was designed as a superiority trial rather than a noninferiority trial. Thus, we cannot exclude the possibility that there is a small beneficial or harmful treatment effect. Among patients with asthma who have symptoms of gastroesophageal reflux, treatment with proton-pump inhibitors reduces these symptoms but probably has little effect on the asthma. Because diagnostic tests for and drug treatment of gastroesophageal reflux in patients with asthma contribute substantially to the cost of asthma care, limited use of these measures seems warranted.

The presence of asymptomatic gastroesophageal reflux, which was noted in nearly half of our study participants with poorly controlled asthma, was not predictive of a treatment effect, indicating that asymptomatic gastroesophageal reflux may not be a frequent cause of poor asthma control. In addition, the failure of proton-pump inhibitors to improve methacholine reactivity suggests that airway inflammation from microaspiration or esophageal reflexes is not a common contributing mechanism of poor asthma control in patients who have persistent asthma symptoms despite the use of inhaled corticosteroids.

Although the dose of esomeprazole used in this study is highly effective in suppressing gastric acid throughout the day, and is larger than the dose that is routinely prescribed for symptoms of gastroesophageal reflux, it does not prevent alkaline reflux, which may also trigger esophageal reflexes mediating neurogenic inflammation in the airways. On occasion, nocturnal gastric acid breakthrough may occur with even high-dose proton-pump inhibitors, though it does not necessarily lead to reflux in asymptomatic persons. Furthermore, asymptomatic gastroesophageal reflux may have other adverse health consequences, such as the development of Barrett's esophagus and a predisposition to esophageal cancer, that are not related to asthma. Accordingly, the use of ambulatory esophageal pH monitoring in patients with asthma ought to be based on the need to diagnose and treat esophageal disease rather than asthma.

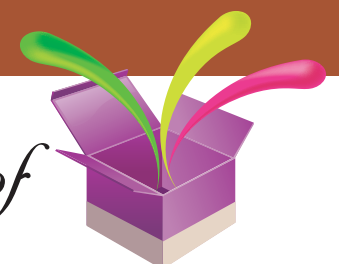
In summary, we have found that there is no benefit of treatment with a proton-pump inhibitor in patients with poorly controlled asthma who have minimal or no symptoms of gastroesophageal reflux. Ambulatory pH monitoring and clinical characteristics do not identify a subgroup that is likely to benefit from such treatment.

Reference : The American Lung Association Asthma Clinical Research Centers

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(May 2017 Volume : 10 Issue : 1)

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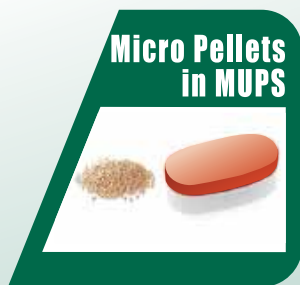
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Editorial Note:

Dear Doctor, It's our immense pleasure to inform you that we have published the second issue, 2017 of *GI Café*. In this issue we try to focus on Efficacy of Esomeprazole for Treatment of poorly controlled asthma. Your comments and suggestions will enrich our upcoming issues. Please participate in quiz competition and win prizes.

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