Effects of 24 Weeks of Lansoprazole Therapy on Asthma Symptoms, Exacerbations, Quality of Life, and Pulmonary Function in Adult Asthmatic Patients With Acid Reflux Symptoms*

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Background: Difficult-to-control asthma has been associated with gastroesophageal acid reflux. Acid-suppressive treatment has been inconsistent in improving asthma control. 

Objective: To determine whether a proton-pump inhibitor improves asthma control in adult asthmatic patients with acid reflux symptoms.

Design: Multicenter, double-blind, randomized, placebo-controlled trial.

Setting: Twenty-nine private practices and 3 academic practices in the United States.

Patients: Two hundred seven patients receiving usual asthma care including an inhaled corticosteroid (ICS). Patients had acid reflux symptoms and moderate-to-severe persistent asthma.

Intervention: Lansoprazole, 30 mg bid, or placebo, bid, for 24 weeks.

Measurements: The primary outcome measure was daily asthma symptoms by diary. Secondary asthma outcomes included rescue albuterol use, daily morning and evening peak expiratory flow, FEV1, FVC, asthma quality of life with standardized activities (AQLQS) questionnaire score, investigator-assessed symptoms, exacerbations, and oral corticosteroid-treated exacerbations.

Results: Daily asthma symptoms, albuterol use, peak expiratory flow, FEV1, FVC, and investigator-assessed asthma symptoms at 24 weeks did not improve significantly with lansoprazole treatment compared to placebo. The AQLQS emotional function domain improved at 24 weeks (p = 0.025) with lansoprazole therapy. Fewer patients receiving lansoprazole (8.1% vs 20.4%, respectively; p = 0.017) had exacerbations and oral corticosteroid-treated (ie, moderate-to-severe) exacerbations (4% vs 13.9%, respectively; p = 0.016) of asthma. A post hoc subgroup analysis revealed that fewer patients receiving one or more long-term asthma-control medications in addition to an ICS experienced exacerbations (6.5% vs 24.6%, respectively; p = 0.016) and moderate-to-severe exacerbations (2.2% vs 17.5%, respectively; p = 0.021) with lansoprazole therapy.

Conclusion: In adult patients with moderate-to-severe persistent asthma and symptoms of acid reflux, treatment with 30 mg of lansoprazole bid for 24 weeks did not improve asthma symptoms or pulmonary function, or reduce albuterol use. However, this dose significantly reduced asthma exacerbations and improved asthma quality of life, particularly in those patients receiving more than one asthma-control medication.

Key words: asthma; exacerbation; gastroesophageal acid reflux; lansoprazole; proton-pump inhibitor

Abbreviations: AQLQS = asthma quality-of-life questionnaire with standardized activities; CI = confidence interval; ICS = inhaled corticosteroid; ICS+ = inhaled corticosteroid plus at least one other long-term asthma-control medication; PPI = proton-pump inhibitor

Difficult-to-control asthma has been associated with gastroesophageal acid reflux, but acid-suppressive treatment has been inconsistent in improving asthma control, as measured by symptoms and pulmonary function.1,2 A metaanalysis1 of randomized controlled trials concluded that therapy for gastroesophageal acid reflux (ie, acid reflux), including acid-suppressive treatment with a proton-pump inhibitor (PPI) or histamine-2 receptor antagonist, does not improve asthma control. However, the previous studies of PPI therapy1 were limited by small numbers of patients, lack of measurement of exacerbations and quality of life, and limited duration of follow-up.

The purpose of this study was to determine whether treatment with 30 mg of lansoprazole (a
PPI), bid for 24 weeks, improved the control of asthma in patients with moderate-to-severe persistent asthma and acid reflux symptoms. We measured daily asthma symptoms by diary as the primary outcome. We measured rescue albuterol use, pulmonary function, asthma quality of life,\(^3\) investigator-assessed asthma symptoms, and asthma exacerbations as secondary outcomes.

**Materials and Methods**

**Patients**

The study was approved by an institutional review board for each of the 32 sites. Three hundred forty-three patients signed informed consent forms and were screened. At screening, patient study inclusion criteria included the following: (1) \(\geq 18\) years of age; (2) investigator-determined history of, or current, symptomatic acid reflux (the presence of acid reflux was based primarily on symptoms of heartburn without preset criteria and was subsequently confirmed by investigator assessment [see “Results” section]; consistent with clinical practice and current guidelines,\(^4\) investigators recruited patients who would typically be given empiric acid-suppressive therapy; however, 24-h esophageal pH monitoring was optional for the confirmation of acid reflux); (3) not taking daily or near-daily acid-suppressive treatment, apart from antacids; (4) moderate-to-severe persistent asthma\(^5\); (5) \(\text{FEV}_1 > 50\%\) predicted and \(< 85\%\) predicted\(^6\); (6) \(\geq 12\%\) improvement in \(\text{FEV}_1\) (in liters) over baseline values after the inhalation of \(180\ \mu\)g of albuterol; (7) not smoking for \(\geq 1\) year with \(< 10\) pack-years of cigarette-smoking history; (8) treatment with an inhaled corticosteroid (ICS); (9) not having marked seasonal variability in asthma or allergy symptoms; (10) reporting five or more nocturnal asthma awakenings during the 4 weeks before screening; and (11) receiving stable doses of asthma medications for at least 4 weeks before screening.

Patients were initially excluded from the study for the following: (1) they were receiving ipratropium bromide or > 10 mg/d prednisone or equivalent; (2) they were receiving astemizole; (3) they were undergoing immunotherapy for < 6 months or were unable to continue receiving the current dose; (4) there was a history of upper respiratory tract infection or hospitalization for asthma within 30 days; hospitalization more than once within 6 months, or any uncontrolled clinically significant medical condition, or (5) they had been treated with a PPI within 14 days of study inclusion, or with an anticoagulant, \(\beta\)-blocker, tricyclic antidepressant, monoamine oxidase inhibitor, or cholinergic agents before screening. Prokinetic agents and histamine-2-receptor antagonists were prohibited after screening.

After the screening and a qualification period, 207 patients were randomized (whites, 93%; African Americans, 3%; others, 4%). The most common reasons for the 136 screening and qualification failures were \(\text{FEV}_1 > 85\%\) predicted, reversibility of \(< 12\%\), or withdrawal of consent.

**Study Design**

The study was conducted from December 22, 1999, to August 8, 2001. Study outline and the disposition of patients are provided in Figure 1. Details of the screening visit, the 15-day qualification period, and the 24-week treatment period are as follows.

**Screening Visit and Qualification Period Procedures**

At the screening visit, patients gave a history and underwent a physical examination, laboratory tests (ie, for measurement of \(\text{FEV}_1\) and FVC), and 12-lead ECG. Patients completed a validated, self-administered asthma quality-of-life questionnaire with standardized activities (AQLQs).\(^3\) After screening, patients were given a diary, an albuterol (Ventolin; GlaxoSmithKline; Research Triangle Park, NC) metered-dose inhaler for as-needed (ie, rescue) use, an antacid (Gelusil; Pfizer; New York, NY) for as-needed use, and a peak flow meter, and entered a 15-day qualification period. Each day, patients recorded daytime and nighttime asthma symptoms, morning and evening peak expiratory flows \(\geq 3\) h after albuterol use, and morning and evening albuterol use. Patients graded daytime and nighttime asthma symptoms on a scale of 0 to 4 (with 4 being most severe), which had been modified from a scale of 0 to 3 points found in published guidelines\(^3\) and had been used in previous studies of asthma.\(^7\) Patients with fewer than two nocturnal awakenings due to asthma symptoms during the qualification period and patients with average daily asthma symptom scores of \(< 1\) (ie, sum of daytime plus nighttime scores/2) on qualification days) were excluded from the study.

**Study Visit Procedures**

Randomization occurred immediately after the 15-day qualification period. At randomization, patients received gray opaque capsules containing 30 mg of lansoprazole or matching gray opaque placebo capsules (1:1 double-blind randomization) to take twice a day, 1 h before breakfast and 1 h before the evening meal. The lansoprazole dose was twice the standard that is commonly used to treat gastroesophageal erosive disease because this dose may be required for acid suppression in asthmatic patients.\(^10\)

Spirometry was performed before and 30 min after 180 \(\mu\)g of inhaled albuterol was administered. The best of three efforts was analyzed. Patients withheld inhaled albuterol therapy for 6 h and the morning dose of all other asthma medications on study days involving spirometry (during screening and randomization, and at 8, 16, and 24 weeks). The AQLQs was performed at screening, and at 4, 8, 12, 16, 20, and 24 weeks. An investigator assessment of asthma and reflux symptoms was performed at randomization, 2 weeks, and at each of the remaining six visits.
Outcome Measures

The screening visit provided baseline values for the AQLQS. The qualification period provided baseline values for asthma diary entries. The randomization visit provided all other baseline values.

The primary outcome measure was the 24-week average of the more severe (range 0 to 4) of each day’s daytime or nighttime asthma symptom score by diary. However, for presentation the average daytime values and average nighttime values are reported. Albuterol use, peak expiratory flow, postbronchodilator administration FVC and FEV₁, AQLQS score, investigator assessments, and exacerbations were secondary outcome measures.

There are 32 questions in four domains (symptoms, activity limitation, emotional function, and environmental stimuli) in the AQLQS. Answers were graded on a scale of 1 to 7 (with 7 being best). The average score of the 32 answers (i.e., overall AQLQS score) and the average of the answers for each domain were calculated separately.

Investigator assessment of asthma and reflux symptoms on a scale of 1 (none), 2 (mild), 3 (moderate), and 4 (severe) included the following: wheezing; chest tightness; dyspnea; worsening asthma symptoms after eating a big meal; heartburn; gastroesophageal regurgitation; dysphagia; belching; hoarseness; globus sensation; overall asthma symptoms; and overall reflux symptoms.

We defined an asthma exacerbation as an investigator-determined episodic worsening of asthma symptoms compared to baseline. This clinical definition is similar to symptom-based definitions used in other asthma studies⁶ and is consistent with the published guidelines.⁵ We defined moderate-to-severe exacerbations as those requiring oral corticosteroid treatment since those exacerbations are potentially of more clinical significance.

Statistical Analysis

A sample size of 200 patients (100 patients in each treatment group) was estimated to have a 78% power to detect differences between the lansoprazole and placebo groups at a 0.05 (two-tailed test) level for severity of diary symptoms for the entire 24 weeks of the study. The mean ± SD change from baseline in severity of diary symptoms for a 78% power calculation was assumed to be 0.43 ± 0.519 with lansoprazole and 0.25 ± 0.510 with placebo, using normal approximations.

Comparisons of proportions were performed by Fisher’s Exact Test where appropriate (e.g., exacerbations and adverse event rates). With patients whose data were incomplete, the last value carried forward was used except for diary peak-flow measurements when actual data were compared. Cochran-Mantel-Haenszel test statistics were used to compare differences between treatment groups for investigator symptom assessments with baseline scores as the stratum. Comparisons of the mean changes from baseline between treatment groups were performed using the Wilcoxon two-sample test for patient diary results. Comparisons of the mean change from baseline between treatment groups were performed using a two-way analysis of variance with treatment, investigator, and treatment-by-investigator as factors for pulmonary function tests, and with treatment and investigator as factors for the AQLQS (results reported as least-squares mean). Time to first exacerbation was analyzed by log-rank test. The total number of exacerbations was analyzed by a maximum likelihood Poisson regression, with treatment duration as an offset variable. All statistical analyses were performed using a statistical software package (SAS, version 6.12; SAS Institute Inc; Cary, NC). Unless indicated, all values are given as the mean (SD). All statistical comparisons were between lansoprazole and placebo. The significance level was set at p ≤ 0.05.

Post hoc Subgroup Analysis

During poststudy data analysis, we noted that most asthma exacerbations occurred in patients receiving an ICS plus another long-term asthma-control medication (e.g., inhaled salmeterol, an oral leukotriene modifier, and/or sustained-release theophylline). For this reason, we conducted a post hoc analysis of lansoprazole vs placebo in patients receiving an ICS plus at least one other asthma-control medication (i.e., the ICS+ subgroup) and in patients receiving an ICS alone (i.e., the ICS subgroup).

Results

Baseline Characteristics and Medication Compliance

During the 2 weeks before screening, 48% of the patients who had been randomized to receive lanso-
prazole and 52% of the patients randomized to receive placebo reported taking an allowed antireflux medication. None underwent 24-h esophageal pH monitoring. At randomization, 97% of patients receiving lansoprazole and 95% receiving placebo had heartburn; 80% of patients in both groups had gastroesophageal regurgitation, and 32% of patients receiving lansoprazole and 47% of patients receiving placebo had dysphagia (p = 0.036). Apart from the less than mild dysphagia (score < 1), there were no significant baseline differences between patients receiving lansoprazole or placebo (Table 1). The mean percentage of compliance with study medication based on pill counts was 96.1 ± 8.0% and 97.3 ± 5.2%, respectively, with lansoprazole and placebo.

**Diary Entries, Spirometry, AQLQS, and Investigator Assessment of Symptoms in Patients Receiving Lansoprazole Compared to Placebo**

Daily asthma symptoms by diary (primary outcome), rescue albuterol use, morning and evening peak expiratory flow, FEV₁, FVC, and overall AQLQS score (Table 1), and the symptoms, activity limitation, and environmental stimuli domains of the AQLQS did not improve significantly. The emotional function domain of the AQLQS improved significantly. Investigator-assessed overall reflux symptoms, heartburn, and gastroesophageal regurgitation improved significantly (Table 1). All other investigator-assessed symptoms did not improve significantly.

**Asthma Exacerbations**

Eight patients receiving lansoprazole had 12 exacerbations (seven patients with 1 exacerbation, and one patient with 5 exacerbations). Twenty-two patients receiving placebo had 27 exacerbations (17 patients with 1 exacerbation, and 5 patients with 2 exacerbations). Significantly fewer patients receiving lansoprazole experienced exacerbations (Fig 2). The odds ratio was 2.9 (95% confidence interval [CI], 1.2 to 6.9). Four patients receiving lansoprazole experienced eight moderate-to-severe exacerbations (three

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**Table 1—Baseline and 24-Week Asthma Diary Symptoms and Selected Secondary Outcomes***

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline Placebo, bid (n = 108)</th>
<th>Lansoprazole, 30 mg bid (n = 99)</th>
<th>24 Weeks Placebo, bid (n = 108)</th>
<th>Lansoprazole, 30 mg bid (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>45 (13)</td>
<td>47 (12)</td>
<td>355 (88)</td>
<td>366 (77)</td>
</tr>
<tr>
<td>Sex, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>67</td>
<td>67</td>
<td>2.7 (0.7)</td>
<td>2.6 (0.6)</td>
</tr>
<tr>
<td>Male</td>
<td>33</td>
<td>33</td>
<td>83 (13)</td>
<td>82 (12)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.4 (7.2)</td>
<td>30.5 (6.7)</td>
<td>3.8 (1.1)</td>
<td>3.6 (0.9)</td>
</tr>
<tr>
<td>Asthma diary symptoms day†</td>
<td>1.50 (0.55)</td>
<td>1.51 (0.55)</td>
<td>3.0 (3.1)</td>
<td>3.6 (3.2)</td>
</tr>
<tr>
<td>Asthma diary symptoms at night†</td>
<td>1.32 (0.52)</td>
<td>1.38 (0.58)</td>
<td>1.18 (0.59)</td>
<td>1.20 (0.57)</td>
</tr>
<tr>
<td>Albuterol use,‡ No. of puffs</td>
<td>4.5 (3.1)</td>
<td>4.3 (2.6)</td>
<td>0.90 (0.57)</td>
<td>1.03 (0.62)</td>
</tr>
<tr>
<td>PEFR, L/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning</td>
<td>355 (88)</td>
<td>366 (77)</td>
<td>2.7 (0.7)</td>
<td>2.6 (0.6)</td>
</tr>
<tr>
<td>Evening</td>
<td>369 (91)</td>
<td>377 (80)</td>
<td>83 (13)</td>
<td>82 (12)</td>
</tr>
<tr>
<td>FEV₁ post-BD</td>
<td>2.7 (0.7)</td>
<td>2.6 (0.6)</td>
<td>3.8 (1.1)</td>
<td>3.6 (0.9)</td>
</tr>
<tr>
<td>% predicted</td>
<td>83 (13)</td>
<td>82 (12)</td>
<td>95 (16)</td>
<td>91 (14)</td>
</tr>
<tr>
<td>FVC post-BD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>2.7 (0.7)</td>
<td>2.6 (0.6)</td>
<td>3.7 (1.1)</td>
<td>3.6 (0.9)</td>
</tr>
<tr>
<td>% predicted</td>
<td>83 (13)</td>
<td>82 (12)</td>
<td>95 (16)</td>
<td>91 (14)</td>
</tr>
<tr>
<td>AQLQS,§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>4.3 (0.11)</td>
<td>4.2 (0.12)</td>
<td>5.0 (0.13)</td>
<td>5.1 (0.14)</td>
</tr>
<tr>
<td>Emotion</td>
<td>4.3 (0.15)</td>
<td>4.1 (0.16)</td>
<td>4.9 (0.17)</td>
<td>5.1 (0.18)</td>
</tr>
<tr>
<td>Overall asthma symptoms¶</td>
<td>1.56 (0.53)</td>
<td>1.57 (0.56)</td>
<td>1.35 (0.65)</td>
<td>1.21 (0.58)</td>
</tr>
<tr>
<td>Overall reflux symptoms¶</td>
<td>1.70 (0.65)</td>
<td>1.66 (0.69)</td>
<td>0.98 (0.85)</td>
<td>0.68 (0.65)#</td>
</tr>
<tr>
<td>Heartburn¶</td>
<td>1.72 (0.74)</td>
<td>1.75 (0.80)</td>
<td>1.03 (0.93)</td>
<td>0.49 (0.68)**</td>
</tr>
<tr>
<td>Regurgitation¶</td>
<td>1.27 (0.83)</td>
<td>1.31 (0.89)</td>
<td>0.75 (0.86)</td>
<td>0.51 (0.69)#</td>
</tr>
<tr>
<td>Dysphagia¶</td>
<td>0.70 (0.83)</td>
<td>0.46 (0.75)</td>
<td>0.45 (0.77)</td>
<td>0.29 (0.58)</td>
</tr>
</tbody>
</table>

*Values are given as the mean (SD), unless otherwise indicated. post-BD = post-bronchodilator (ie, after the inhalation of 180 μg of albuterol from a metered-dose inhaler); PEFR = peak expiratory flow rate. Comparisons between treatments were not significant except as noted.

†Scale of 0 to 4, with 4 being the most severe.

‡Day and night values combined.

§Values given as the mean (SE).

||p < 0.05.

¶An investigator-assessed scale was used, as follows: 0, none; 1, mild; 2, moderate; and 3, severe.

#p < 0.01.

**p < 0.001.**
patients with one exacerbation, and one patient with five exacerbations). Fifteen patients receiving placebo experienced 19 moderate-to-severe exacerbations (11 patients with 1 exacerbation, and 4 patients with 2 exacerbations). Significantly fewer patients taking lansoprazole experienced moderate-to-severe exacerbations (Fig 2). The odds ratio was 3.8 (95% CI, 1.2 to 12.0).

Patients receiving lansoprazole had a significant increase in the time to first exacerbation (Fig 3) and the time to first moderate-to-severe exacerbation ($p < 0.013$, data not shown). Further, there was a significant reduction in the total number of exacerbations and the total number of moderate-to-severe exacerbations with lansoprazole when treatment duration was used as an offset variable ($p = 0.021$ and 0.041, respectively).

Post hoc Subgroups Baseline Characteristics

Of 103 ICS+ subgroup patients, 46 received lansoprazole and 57 received placebo. Of 104 ICS subgroup patients, 53 received lansoprazole and 51 received placebo. Baseline values did not differ significantly between the lansoprazole and placebo groups in either the ICS+ or the ICS subgroups except that the mean FVC was higher in the ICS subgroup patients receiving placebo (95.6 ± 17.4% predicted vs 89.3 ± 11.7% predicted, respectively; $p < 0.05$).

Post Hoc Subgroups Results in Patients Receiving Lansoprazole Compared to Those Receiving Placebo

Apart from significant improvement in investigator-assessed heartburn ($p < 0.05$), there were no significant findings in the ICS subgroup. In the ICS+ subgroup, daily asthma symptoms by diary, rescue albuterol use, morning and evening peak expiratory flow, FEV$_1$, and FVC did not improve significantly (data not shown). Overall AQLQS, symptoms, and emotional function domains improved significantly at 20 weeks and 24 weeks (range, $p = 0.023$ to 0.009); the activity limitation domain improved significantly at 20 weeks ($p = 0.036$). At 24 weeks, minimal important improvement ($> 0.5$)$^{16}$ was reached in the overall AQLQS score, the symp-
tom domain, and the emotional function domain (0.6, 0.7, and 0.7 respectively). Overall investigator-assessed asthma symptoms, overall reflux symptoms, heartburn, and regurgitation improved significantly (p < 0.05) at 24 weeks (data not shown). Fewer ICS+ subgroup patients receiving lansoprazole experienced exacerbations. Odds ratios for exacerbations and moderate-to-severe exacerbations were 4.7 (95% CI, 1.3 to 17.4; p = 0.016) and 9.6 (95% CI, 1.2 to 77.9, respectively; p = 0.021).

**Asthma Medication Changes**

Apart from treatment for acute exacerbations, five lansoprazole patients and five placebo patients had an asthma medication change during the study.

**Adverse Events**

A similar percentage of patients receiving lansoprazole or placebo experienced any treatment-emergent adverse event over the 24 weeks of treatment (74% and 69%, respectively). Significantly more patients receiving lansoprazole reported diarrhea (10% vs 3%, respectively) and infection (7% vs 0%, respectively). The percentages of severe adverse events were similar in the lansoprazole and placebo groups (8% vs 6%, respectively). Possibly, probably, or definitely treatment-related adverse events occurred in significantly more lansoprazole patients (13% vs 4%, respectively; p = 0.020).

**DISCUSSION**

This large randomized, placebo-controlled trial demonstrated that 24 weeks of treatment with lansoprazole did not reduce daily asthma symptoms and albuterol use, or improve pulmonary function in asthmatic patients with symptoms of acid reflux. However, we think that this is the first randomized study to suggest that PPI treatment reduces exacerbations. In addition, this study suggests that asthmatic patients receiving lansoprazole had improvement in asthma quality of life. Further, a post hoc analysis suggested that asthmatic patients receiving more than one asthma-control medication had a greater benefit from lansoprazole (ie, had a greater reduction in the number of exacerbations and a greater improvement in quality of life).

The lack of improvement with lansoprazole treatment in terms of asthma symptoms and pulmonary function is in keeping with the mixed results of six previous smaller (≤ 57 patients) and shorter term (≤ 3 months) randomized studies of a PPI (omeprazole) as presented in a metaanalysis. For example, two studies had no significant findings, three studies had one significant finding each of improvement in
asthma symptoms, FEV1, or evening peak expiratory flow, and one study had improvement in asthma symptoms and morning peak expiratory flow.

Exacerbations, which were identified by investigators as an increase in episodic asthma symptoms, were reduced in patients receiving lansoprazole. In contrast, the significant reduction in exacerbations with lansoprazole was not accompanied by a significant reduction in the average number of daily asthma symptoms as recorded by the patients in a diary. We suggest that the 24 weeks of this study allowed time to collect a sufficient number of exacerbations in patients receiving placebo for the detection of significant improvement with lansoprazole. However, on most days there would be no exacerbations during the 24 weeks. We speculate that the minority of days with exacerbations did not significantly contribute to the average daily number of asthma symptoms in patients receiving placebo, leading to no significant difference compared to patients receiving lansoprazole.

Only one previous randomized study17 has examined asthma quality of life with treatment using a PPI (omeprazole) in asthma patients. The improvement in the emotional function domain score of the AQLOs in our study is consistent with improvement in quality of life in the previous study of nine asthmatic patients.

The reason that some patients were receiving more than one asthma-control medication and appeared to have greater benefit from lansoprazole requires further study. These patients may have required the asthma medications in their treatment to improve chronic asthma symptoms from substantial acid reflux. However, these medications may have been less successful in preventing episodic worsening of asthma symptoms and consequent worsening of quality of life unless the patients were being treated with lansoprazole. This speculation is consistent with studies10,18,19 suggesting that a greater degree of acid reflux is associated with a greater frequency of asthma symptoms, which may be improved with a PPI.

The role of acid reflux treatment in the management of asthma is undefined. Previous analyses have suggested a place for the empiric treatment of acid reflux with a standard PPI dose for erosive disease for 3 months to improve asthma control. In those patients whose asthma is not improved, 24-h esophageal pH monitoring was recommended to guide further medical therapy.30 There may also be a role for surgical treatment to prevent acid reflux and to improve asthma control, as has been suggested by two randomized trials.2,21

The dose of lansoprazole in this study is likely to suppress gastric acid with normalization of esophageal acid exposure in up to 100% of patients with acid reflux.22 While there is no direct information on acid suppression with lansoprazole therapy in asthmatic patients, a comparable dose of omeprazole23 suppressed acid reflux in 93% of 30 asthmatic patients.10

This study suggests that some consideration also should be given to empiric treatment at some point administering twice the standard PPI dose for erosive disease for 24 weeks, particularly in asthmatic patients receiving more than one asthma-control medication. This suggested consideration is based on the expectation of a high degree of acid suppression, and the reduction in exacerbations and improvement in quality of life, particularly in the ICS+ subgroup. The clinical evaluation may include information regarding exacerbations and interview assessment of overall asthma and reflux symptoms, since these were most consistently reduced in patients receiving lansoprazole in the ICS+ subgroup.

Esophageal pH monitoring is the most specific means of identifying acid reflux20 and is likely to have identified a higher proportion of patients whose asthma would improve with PPI therapy than was observed in this study. However, a negative pH study result may potentially exclude 10 to 30% of patients with symptomatic acid reflux who may benefit from such therapy.20

This study has several limitations. The reduced number of exacerbations and improved quality of life were secondary outcomes. The greater benefit in asthmatic patients receiving more than one asthma-control medication was based on a post hoc analysis. Because of the limitations of this study, further studies using exacerbations and quality-of-life measures should be conducted for confirmation in similar populations and other study populations (eg, patients with more severe or variable asthma and/or more or even less symptomatic acid reflux). In addition, future studies are needed to determine the most effective PPI dose and treatment duration to help maintain control of asthma.

In conclusion, a dosage of 30 mg of lansoprazole bid for 24 weeks did not result in the improvement of daily asthma symptoms, rescue albuterol use, or pulmonary function in patients with moderate-to-severe persistent asthma and acid reflux symptoms compared to placebo. However, this dose significantly reduced asthma exacerbations and improved some aspects of asthma quality of life. Greater benefits with lansoprazole appeared to occur in asthmatic patients receiving more than one asthma-control medication.

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APPENDIX

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