Influence of Age on Treatment With Proton Pump Inhibitors in Patients With Laryngopharyngeal Reflux Disease: A Prospective Multicenter Study

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**IMPORTANCE** Several trials on the predictors of response to proton pump inhibitor (PPI) treatment of laryngopharyngeal reflux (LPR) have shown conflicting results. Furthermore, the influence of age in disease severity and response to PPI therapy is unclear.

**OBJECTIVE** To assess the difference in disease severity and response to PPI therapy according to age in patients with LPR.

**DESIGN, SETTING, AND PARTICIPANTS** Prospective multicenter study at 3 tertiary medical centers of 264 consecutive patients with LPR who were referred to the otolaryngology clinic from November 2010 to February 2012.

**INTERVENTIONS** Participants were prescribed 15 mg of lansoprazole (PPI) twice daily for 3 months.

**MAIN OUTCOMES AND MEASURES** Reflux Symptom Index (RSI), Reflux Finding Score (RFS), and laryngopharyngeal reflux-health-related quality of life (LPR-HRQOL) were collected at baseline and at 1 and 3 months postbaseline.

**RESULTS** After 3 months, 35 patients were lost to follow-up and excluded; the remaining 229 patients included 135 men and 94 women. The oldest group (60-79 years; n = 111) showed higher baseline RSI (P < .001) and LPR-HRQOL (P < .001) scores than the 18- to 39-year-old (n = 35) and 40- to 59-year-old (n = 83) groups. However, baseline RFS scores showed no significant difference among age groups (P = .44). Within each age group, the RSI, RFS, and LPR-HRQOL improved significantly with PPI therapy (all P < .001); however, no significant difference in improvement of RSI (P = .59), RFS (P = .50), or LPR-HRQOL (P = .09) was seen among the groups. At 3-month follow-up, significantly more responders, defined as those whose RSI score improved by more than 50%, were found in the 18- to 39-year-old and 40- to 59-year-old groups (86% and 75%, respectively) than in the oldest group (57%) (P = .002), but there was no significant difference in proportion of responders among age groups at 1-month follow-up (P = .69).

**CONCLUSIONS AND RELEVANCE** In patients with LPR, age seems to affect the subjective symptoms and resulting impact on quality of life but not the laryngeal findings. Furthermore, older patients are more likely not to respond to PPI therapy than younger patients.

Laryngopharyngeal reflux (LPR) refers to the retrograde flow of stomach contents into the throat and larynx, which leads to symptoms such as chronic dysphonia, throat clearing, cough, globus sensation, and sore throat. In otolaryngologic practice, approximately 10% of patients presenting to outpatient clinics and more than 50% of patients with voice problems receive a diagnosis of LPR. Laryngopharyngeal reflux is a gastrointestinal and otolaryngological condition related to but distinct from gastroesophageal reflux disease (GERD). The reflux of gastric contents is at the core of both LPR and GERD, but the mechanism and symptoms of the 2 disorders are different. The laryngeal mucosa are vulnerable to exposure to acidic substances, so patients often present with laryngopharyngeal symptoms without heartburn or regurgitation. Several studies have suggested that the frequency of GERD complications (esophagitis, Barrett esophagus, stricture) is higher in geriatric patients because of many potential aggravating factors; however, the influence of age in LPR is unclear. Although a 3-month empirical trial of proton pump inhibitor (PPI) treatment is generally regarded as a cost-effective modality for the initial management of LPR, the difference in response to PPI therapy according to age is not established. Garrigues et al. suggested that response to therapy was associated with younger age and shorter duration of laryngeal symptoms, but the response could not consistently be predicted in patients with chronic posterior laryngitis.

Thus, we conducted a prospective cohort study to assess the difference in symptom severity according to age in patients with LPR through the Reflux Symptom Index (RSI). Reflux Finding Score (RFS), and laryngopharyngeal reflux-health-related quality of life (LPR-HRQOL) score. Furthermore, we evaluated the influence of age on response to PPI therapy.

Methods

Subjects and Study Design

Patients with suspected LPR who were referred to 3 different otolaryngology clinics from November 2010 to February 2012 were assessed for eligibility for the study. All patients underwent otolaryngologic evaluation by 1 of us (S.W.K., K.H.K., Y.G.E.), including laryngoscopy and video strobolaryngoscopy. Diagnosis of LPR was made on the basis of the presence of at least 1 of the following symptoms: hoarseness, chronic cough, throat irritation, laryngospasm, chronic throat clearing, and dysphasia. Diagnosis of LPR was also based on confirmed signs such as erythema, vocal cord edema, subglottic edema, posterior pachydermia, laryngeal edema, ventricular obliteration, and thick endolaryngeal mucus and granuloma from the findings of the laryngoscope. Last, diagnosis required that symptoms not be due to laryngitis caused by upper airway infections and/or allergies. A consensus meeting among the 3 otolaryngologists was conducted to improve interrater reliability. The enrolled participants included all the patients who initially received a diagnosis of LPR and had no history of PPI treatment. Patients younger than 18 years, those experiencing GERD symptoms but not LPR symptoms, and those who had a malignant tumor or major psychosis were excluded. The study protocol was reviewed and approved by the institutional review boards of Kyung Hee University Hospital at Gangdong, Seoul Veterans Hospital, and Samsung Changwon Hospital. Written informed consent was obtained from the participants.

In addition to advice about lifestyle modification (avoidance of caffeine, alcohol, smoking, fatty food, and eating close to bedtime), patients with LPR were prescribed 15 mg of lansoprazole 2 times a day for 3 months. Patients were instructed to take the PPI 30 minutes before meals. The disease severity and changes in subjective symptoms were assessed using 2 surveys, the RSI and LPR-HRQOL, for 3 months.

The surveys were administered 3 times during this period at outpatient department visits: the first visit and follow-up visits at 1 and 3 months. In addition, to evaluate the objective findings of the laryngeal condition, the RFS by Belafsky et al. was conducted by an otolaryngologist. A greater than 50% primary RSI improvement from baseline was considered a response to PPI therapy.

The Questionnaires

The RSI is a high validity survey that not only assesses the level of severity of LPR but also includes 9 questions to estimate the response to treatment. The questionnaire evaluates the level of symptoms and their severity through a 6-point Likert scale, which ranges from 0 to 5. A high score indicates that patients have more severe symptoms, whereas 0 indicates the absence of symptoms.

The LPR-HRQOL, developed by Carru et al., has been shown to be a reliable and valid rating scale for evaluating the quality of life (QOL) of LPR patients. It consists of a simple questionnaire of 43 questions in the 5 categories of hoarseness, cough, throat clearing, swallowing, and overall impact of acid reflux. The questionnaire consists of basic 7-point Likert scale questions in the first 4 categories and concludes with a 10-point Likert scale question regarding the overall impact of acid reflux. A high score indicates that patients have more severe symptoms, whereas 0 indicates the absence of symptoms.

Examination of the Larynx

All enrolled participants underwent laryngoscopy to evaluate objective signs of LPR on the basis of the RFS. An otolaryngologist performed the examination using a strobolaryngoscope, and 70° rigid endoscopes were generally used. When the vocal cords and surrounding structures were not clearly visible in the rigid endoscope, a flexible nasopharyngoscope was used to increase accuracy. Participants were instructed to verbalize “yee” in a high-pitched tone, low-pitched tone, and regular-pitched tone. Through this procedure, the diagnosis of LPR and the RFS, the rating scale of clinical advanced LPR, were assessed. The RFS ranged from 0 (normal state) to 26; a higher score indicates a deteriorated laryngeal condition. A consensus meeting among the 3 clinics was conducted to improve the interrater and intrarater reliability in RFS scoring. This investigation was performed according to standard protocol and scored by observers blinded to the patient’s identity.
Statistical Analysis
For statistical analysis, SPSS, version 18.0 (SPSS), was used, and all of the data are presented as mean (SD). A t test and analysis of variance (ANOVA) were used to compare age differences in RSI, RFS, and LPR-HRQOL data. A repeated measure of ANOVA was used to determine which age group showed a greater response to PPI therapy. An ANOVA model in repeated measures at 3 time points was used with Bonferroni correction for multiple comparisons. Comparison of the proportion of responders according to age was made using a χ² analysis. A difference was considered statistically significant when the P value was less than .05.

Results
Study Populations
Of 264 consecutive patients considered for the study, 35 were excluded because of loss of follow-up at 3 months. A total of 229 patients with LPR were enrolled and completed the study without loss to follow-up. There were 135 men (59.0%) and 94 women (41.0%). The mean (SD; range) age of the patients was 55.7 (14.0; 18-79) years. Patients were divided into 3 age groups of 18 to 39, 40 to 59, and 60 to 79 years. The number of patients in each group was 35 (15.3%), 83 (36.2%), and 111 (48.5%), respectively.

Table 1. Initial Reflux Symptom Index (RSI), Reflux Finding Score (RFS), and LPR–Health-Related Quality of Life (LPR-HRQOL) According to Age Group

<table>
<thead>
<tr>
<th>Test</th>
<th>Score, Mean (SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18-39 y (n = 35)</td>
<td>40-59 y (n = 83)</td>
</tr>
<tr>
<td>RSI</td>
<td>13.88 (7.68)</td>
<td>12.20 (8.90)</td>
</tr>
<tr>
<td>RFS</td>
<td>6.78 (4.86)</td>
<td>7.18 (4.55)</td>
</tr>
<tr>
<td>LPR-HRQOL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voice</td>
<td>14.48 (18.65)</td>
<td>18.63 (21.36)</td>
</tr>
<tr>
<td>Cough</td>
<td>6.42 (7.36)</td>
<td>8.96 (7.36)</td>
</tr>
<tr>
<td>Throat clearing</td>
<td>6.97 (7.99)</td>
<td>6.15 (7.22)</td>
</tr>
<tr>
<td>Swallowing</td>
<td>6.05 (7.25)</td>
<td>6.40 (6.38)</td>
</tr>
<tr>
<td>Overall impact of acid reflux</td>
<td>21.28 (18.46)</td>
<td>21.45 (14.72)</td>
</tr>
</tbody>
</table>

Table 2. Improvement in Reflux Symptom Index (RSI), Reflux Finding Score (RFS), and LPR–Health-Related Quality of Life (LPR-HRQOL) After Proton Pump Inhibitor Therapy According to Age

<table>
<thead>
<tr>
<th>Test</th>
<th>Score, Mean (SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 Month</td>
</tr>
<tr>
<td>RSI</td>
<td>18-39 y</td>
<td>13.88 (7.68)</td>
</tr>
<tr>
<td></td>
<td>40-59 y</td>
<td>12.20 (8.90)</td>
</tr>
<tr>
<td></td>
<td>60-79 y</td>
<td>18.45 (10.43)</td>
</tr>
<tr>
<td>RFS</td>
<td>18-39 y</td>
<td>6.21 (4.87)</td>
</tr>
<tr>
<td></td>
<td>40-59 y</td>
<td>6.46 (4.70)</td>
</tr>
<tr>
<td></td>
<td>60-79 y</td>
<td>7.74 (3.92)</td>
</tr>
<tr>
<td>LPR-HRQOL</td>
<td>18-39 y</td>
<td>21.50 (19.29)</td>
</tr>
<tr>
<td></td>
<td>40-59 y</td>
<td>20.81 (14.50)</td>
</tr>
<tr>
<td></td>
<td>60-79 y</td>
<td>35.20 (23.29)</td>
</tr>
</tbody>
</table>

Difference of RSI, RFS, and LPR-HQOL According to Age
The oldest patient group (60-79 years) with LPR had significantly higher mean (SD) baseline RSI scores than the 18- to 39-year-old and 40- to 59-year-old patient groups (18.45 [10.43] vs 13.88 [7.68] and 12.20 [8.90], respectively; P < .001). However, the RFS score showed no significant difference among age groups. The oldest patient group showed significantly worse results on all domains of the LPR-HRQOL (all P < .001) (Table 1).

Improvement of RSI, RFS, and LPR-HRQOL After PPI Therapy
Within each age group, scores on all 3 tests improved significantly during the period of PPI therapy; however, there was no significant difference among groups in the amount of improvement (RSI, P = .59; RFS, P = .50; LPR-HRQOL, P = .09) (Table 2).

Difference in Proportion of Responders on RSI According to Age
Among the age groups, the proportion of responders, as evaluated by RSI score, showed no significant difference at 1 month; however, responders were significantly more plentiful in the 2 younger groups than the oldest group at 3 months (P = .002) (Table 3).
Table 3. Proportion of Responders as Evaluated by Reflux Symptom Index (RSI) According to Age

<table>
<thead>
<tr>
<th>Follow-up Period, mo</th>
<th>18-39 y (n = 35)</th>
<th>40-59 y (n = 83)</th>
<th>60-79 y (n = 111)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11 (31)</td>
<td>26 (31)</td>
<td>41 (37)</td>
<td>.70</td>
</tr>
<tr>
<td>3</td>
<td>30 (86)</td>
<td>62 (75)</td>
<td>63 (57)</td>
<td>.002</td>
</tr>
</tbody>
</table>

*Responders were defined as those whose RSI score improved by more than 50% after proton pump inhibitor therapy.

Discussion

The major finding of this prospective study is that the subjective severity of LPR is significantly greater in older than in younger patients. In addition, the older patients showed lower response rates after PPI therapy.

In a previous cohort study in 100 patients with no history of voice or laryngeal symptoms, 35% were found to have symptoms of LPR and 64% showed 1 or more physical findings of LPR on laryngoscopic examination.27 Despite the high prevalence of LPR, there are few data on the influence of age on symptom severity or response to PPI treatment. The present prospective study investigated the influence of age on severity and PPI response in LPR. We assessed the subjective severity through the LPR-HQQL, which evaluated the QOL of patients with LPR, as well as the RSI in groups stratified according to age. To our knowledge, this is the first report of greater severity of disease and negative impact on QOL in geriatric patients with LPR.

It is known that the incidence of GERD symptoms does not increase with age; however, several studies suggest that the frequency of GERD complications such as esophagitis, stricture, or Barrett esophagus is significantly higher in older people.5,7,13,14 The most likely reason for the increased severity of GERD in older people is the cumulative injury of acid to the esophageal mucosa over time. In addition, a defective antireflux barrier, abnormal esophageal clearance, altered esophageal mucosal resistance, and delayed gastric emptying could contribute to this phenomenon.15

It is not known whether the severity of LPR in older patients is greater than in younger patients. Saruç et al19 demonstrated that age is not a risk factor for the development of LPR. Our results, older patients with LPR showed a higher score on the RSI. Moreover, LPR symptoms had a significantly greater negative impact on the lives of older patients. In a recent study on the QOL impact of LPR, LPR symptoms had a significant correlation with all tested QOL parameters.17 However, we could not find any difference in RFS, the objective laryngeal finding, among the groups. Our data suggest that age affects the subjective symptoms and resulting impact on the QOL in LPR but not the laryngeal finding. The difference may be the result of a different perspective on their health status among people of different ages.

Many previous studies agree that PPI therapy is the cornerstone of LPR treatment.18,19 The current management strategy for patients with LPR is empirical therapy with a twice-daily PPI for 3 months20; however, the proportion of patients who respond to PPI therapy varies, ranging from 27% to 83% for 1 month of treatment and 41% to 100% for 3 months of treatment.20-22 Although several randomized clinical trials demonstrated no significant postintervention difference between groups receiving a PPI vs placebo, in a recent open-label observational study, significant improvement in RSI (primary RSI improvement of >50%) was obtained in 75% of patients after 12 weeks.23 This is similar to the response rate in the 40- to 59-year-old group in our study. Moreover, we were able to find a difference in response among the groups according to age. This is a noteworthy finding in our trial, although there was no placebo group.24

Several trials on the predictors of response to PPI treatment have also shown conflicting results. Park et al24 demonstrated that pretherapy abnormalities in the interarytenoid mucosa and true vocal fold were associated with a 2-fold increase in symptom response to PPI treatment. Williams et al25 reported that neither baseline GERD symptoms nor endoscopic findings predicted laryngoscopic or symptomatic response. Another study suggested that baseline anxiety levels and heartburn scores and medication dose might be relevant factors in predicting faster response to PPI treatment in carefully selected patients.26 In our data, different age groups had different proportions of responders as evaluated by the RSI. The response rate in the oldest patients was significantly lower than in other age groups.

Few published articles have investigated PPI resistance in LPR. Amin et al27 suggested that incomplete suppression might result from a shorter duration of drug action in unresponsive patients, possibly through increased metabolism of the PPI by the liver. Another explanation for poor response to PPI therapy is low bioavailability of the drug. Ashida et al28 suggested that decreased plasma levels of PPI in patients with resistant gastric ulcers were due to an increase in gastric emptying time. Several authors have shown that older adults have a significant decrease in the amplitude of peristaltic pressures.29-31 This is associated with a higher prevalence of diabetes mellitus or rheumatological disorders, which may alter esophageal motility in older persons. Therefore, decreased acid clearance in geriatric patients might be a possible cause of decreased response to PPI therapy.

Limitations of the present study include the lack of a placebo group as control. Moreover, we did not demonstrate the reflux events by means of multichannel impedance or pH monitoring studies. Although the gold standard diagnostic method for LPR is dual-probe 24-hour pH monitoring, it is an invasive test with a high false-negative rate.23 Also, LPR is a fluctuating condition and there can be substantial day-to-day variation of acid exposure in the hypopharynx.32 However, the response to PPI therapy in patients with suspected LPR is usually so explicit that empirical PPI therapy in LPR is recommended by both gastroenterology and otolaryngology experts and guidelines.33,34 The present study might have meaningful implications for the difference in the effects of PPI therapy according to age.
Although there was no significant difference in the objective findings among the different age groups, the subjective severity of LPR in geriatric patients is significantly greater than in younger patients. Furthermore, older patients are more likely not to respond to PPI therapy than younger patients.

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Author Contributions: Dr Eun had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Y. C. Lee, J. S. Lee, Kim, Kwon, Eun.

Drafting of the manuscript: Y. C. Lee, J. S. Lee.
Critical revision of the manuscript for important intellectual content: Kim, Kwon, Eun.
Study supervision: Kim, Kwon, Eun.

Conflict of Interest Disclosures: None reported.

REFERENCES