RELIEVING LARYNGOPHARINGERAL REFLUX (RELIEF) SURVEY IN OTOLARYNGOLOGY - II THE VIEWPOINT OF THE PATIENT

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As LPR diagnostic work-up is complex in the absence of a definitive gold standard diagnostic test, patient symptoms have become a primary method to identify those with LPR. In this regard, Reflux Symptom Index (RSI) is a reliable self-administered questionnaire useful also to monitor changes after treatment. An Italian survey on patients with LPR evaluated the effect of treatments for LPR that were prescribed in a real-world setting, such as Otolaryngological clinics. In this part of the survey, 1,680 subjects [45.2% males, 54.8% females, 50.4 (14.7) years] were visited in the 86 Italian ORL centers. About 70% of patients were treated with Marial® alone, 27% with PPI plus add-on. RSI change assessment was the primary outcome. Both therapeutic options significantly ($p<0.0001$) reduced RSI score interestingly since the second week. The inter-group comparison demonstrated the Marial® monotherapy induced a greater reduction of RSI than PPI plus add-on since the second week. In conclusion, the present survey reported that a new medical device (Marial®) may be considered a valid option for the treatment of LPR.

Laryngopharyngeal reflux (LPR) is an extra-esophageal manifestation of gastroesophageal reflux disease (GERD) as stated by the Montreal Consensus (1). GERD epidemiological prevalence is worldwide increasing (2, 3). Consistently, the number of patients who are aware of unusual sensations in the laryngopharynx with GERD is also increasing (4, 5). LPR has a relevant impact in otolaryngologist practice: up to 50 % of patients with voice complaints could have LPR (6). Moreover, LPR has been associated with several disorders, including reflux laryngitis and reflux cough. Symptoms associated with reflux laryngitis are hoarseness, throat clearing, choking sensation, dysphagia, dysphonia, laryngeal globus, sore throat, and laryngospasm. Noteworthy, LPR is not usually associated with esophagitis, heartburn, or regurgitation (7). Since the typical LPR symptoms are nonspecific and can also be caused by infections, vocal abuse, allergy, smoking, inhaled environmental irritants, alcohol abuse, chronic sinusitis, laryngeal cancer, thyroid disorder, drugs, psychosomatic disorder, and depression, increased

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awareness of LPR can lead to overdiagnosis or mysdiagnosis of the disease (4).

The LPR diagnostic work-up is pragmatically based on history, clinical examination, and laryngoscopy. In addition, 24-hour pH monitoring, pepsin assay, digestive endoscopy, and imaging may be considered, but they are usually reserved to complicated patients in clinical practice. On the contrary, protonic pump inhibitor (PPI) test, such as an empiric course of this medication, is very popular in clinic setting. Really, the laryngoscopic examination has low specificity and pH monitoring is poorly sensitive, so the most accepted method in clinical practice to diagnose LPR is a trial of PPI therapy (8). As a diagnostic treatment, the PPI test is performed despite symptoms improving in suspected patients with reflux laryngitis. Altman suggested that empirical PPI therapy for a period of 1-2 months is a reasonable initial approach in patients with LPR symptoms (9). Patients unresponsive to PPI therapy have either non-reflux-related causes or may have a functional component to their symptoms. However, PPIs are overprescribed, expensive, and the safety profile may rise some uncertainty. In this regard, the prescriptive applicability is a mandatory aspect in the best practice. Therefore, even though pathognomonic signs and/or symptoms lack, LPR has become a primary diagnosis and resulted in patients experiencing a barrage of medications, specialty physician visits, diagnostic tests, and surgeries (10, 11). Thus, in the absence of a definitive diagnostic test, patient symptoms have become a primary method to identify those with LPR. Symptomatic differentiation of GERD and LPR should be possible if they indeed have discrete phenotypes (10). Therefore, patient-reported outcome (PRO) measures have become a principal means to diagnose LPR and monitor treatment outcomes.

However, if PRO measures are to be used to make patient-centered, symptom-based diagnosis and treatment decisions, they must be designed with appropriate methodological rigor. Use of poorly developed measures or those intended for a different application can have significant implications and lead to distorted, inaccurate, or equivocal findings (12, 13). While the ability to monitor change in LPR-symptoms or quality of life is an attribute most measures espouse, few instruments adequately demonstrated responsiveness to change. In this context, only two instruments met validity criterion: RSI (reflux symptoms index) and LPR-HRQL (LPR-health related quality of life) as recently evidenced (14, 15). So, patient-reported outcome measures are currently a principle method of diagnosing LPR and monitoring effectiveness of prescribed treatments. In particular, RSI seems to be very feasible and handy, as it is a self-completed questionnaire, consisting of 9 items (14). A score >13 is considered positive for LPR.

LPR treatment is based on two cornerstones: lifestyle modification and medical therapy. Modification of daily lifestyle is relevant in the LPR management. Avoidance of stimuli that may aggravate acid reflux, such as drinking alcohol, smoking, fatty foods, chocolate, acidic foods, spicy foods, and caffeine, is convenient. In addition, to raise the head of the bed during sleep, to avoid eating within 3 h of lying down, to perform adequate physical exercise, and to control the body weight are useful recommendations. Unfortunately, these measures are difficult to be complied and cannot be resolved. Accordingly, medical treatment remains the mainstay in LPR management. PPI and alginates are a common prescribed medication for LPR (17). Indeed PPI response rating is not completely satisfying in a large part of LPR patients, so alginates are commonly used (18). In this regard, a meta-analysis study evidenced that there was no difference between the PPI and placebo groups for LPR, whereas three trials exhibited statistically significant results (16).

A randomized controlled study showed that a liquid alginate suspension could achieve significant improvement in the symptom scores and clinical findings of LPR (19). Alginate has the characteristic of protection of the mucosal tissues from acid and non-acid reflux and displacement of acid pocket away from the oesophagus (20). Interestingly, alginate demonstrated non-inferiority to omeprazole and was as effective as omeprazole for symptomatic relief (21). Furthermore, adding alginate to a PPI can significantly relieve heartburn compared to

using a PPI alone, suggesting an additional benefit of alginate as add-on therapy in the management of refractory symptoms (22). However, these options could be used for long-term schedule, so alternatives should be considered.

As a new medical device has been introduced in the Italian market: Marial® (manufactured by Aurora, Milan, Italy) containing magnesium alginate and E-Gastryal®, an Italian survey explored the pragmatic approach of a group of otorhinolaryngologists in the LPR management. The aim of the current analysis was to evaluate the LPR patient's point of view during a therapy course using the RSI changes as an objective primary outcome.

MATERIAL AND METHODS

The current survey was conducted in 86 Otorhinolaryngological centers, distributed in all of Italy to assure a wide and complete national coverage. The otorhinolaryngologists were recruited to participate in the study. They endorsed to the Project RELIEF (Relieving LPR in Otolaryngology). They were asked to recruit all consecutive patients visited because of upper respiratory symptoms ascribable to a suspected LPR.

Patients were consecutively recruited during the specialist visit. The inclusion criteria were: to have a pragmatic diagnosis of LPR based on positive RSI and RFS scores (respectively >13 and >7) and/or suggestive history, both genders, and adulthood. Exclusion criteria were to have comorbidities able to interfere the evaluation of outcomes. As this survey was based on a real-world practice, doctors had the complete liberty of choosing the preferred medications on the basis of the best practice. Actually, three therapeutic options were prescribed: PPI as monotherapy, Marial® as monotherapy, and PPI plus add-on. The add-options included a miscellany of medication alternatives, including alginates, anti-acids, prokinetics, antiH2, and Marial®.

The treatment course lasted 4 weeks. Medications were taken following the specific indications. Patients were asked to weekly complete RSI questionnaire. Five RSI scores were available: at baseline, after 1, 2, 3, and 4 weeks. They were then collected in the specialist office without a new visit.

RSI was evaluated according to the protocol proposed by Belafsky (10). Items are analytically reported in another article published in the present Supplement.

Demographic and clinical characteristics were described using means with SDs for normally-distributed continuous data (i.e. age) or medians with lower and upper quartiles for not normally-distributed data (i.e. for RSI) or as absolute frequency and percentages for categorical data (i.e. frequency of treatments).

Difference in the median values of each continuous variable between before and after 4 weeks' treatment was evaluated with Wilcoxon signed rank test; when more than two groups were compared (i.e. total RSI weekly trend over time), Kruskal Wallis test, followed by Dunn's test, was used.

Statistical significance was set at $p < 0.05$, and the analyses were performed using GraphPad Prism software, GraphPad Software Inc, CA, USA.

RESULTS

Globally, 1.680 subjects [45.2% males, 54.8% females, 50.4 (14.7) years] were visited in the 86 Italian ORL centers and concluded the treatment course. All subjects completed the RSI questionnaire.

Fig. 1 shows the distribution of the different treatments prescribed by the Otolaryngologists: about 70% of patients were treated with Marial® alone, 27% with PPI plus add-on (almost always with Marial®), while only 7 patients (0.4%) were treated with PPI alone, and 36 patients (2.1%) were treated with a Miscellany option (including alginates, anti-acids, prokinetics, and antiH2).

Fig. 2A shows the median (IQR) RSI value in all patients at baseline and after 4 weeks (i.e. end of the therapy): RSI significantly diminished ($p=0.0001$). Fig. 2B shows the RSI trend over time (such as weekly): there was a significant diminution since the second week ($p<0.0001$).

Fig. 3 shows the trend of the total RSI values in patients treated with Marial® as monotherapy or with PPI plus add-on. Both treatments induced a significant reduction of the total RSI ($p<0.0001$ for both). In addition, Marial® induced a greater reduction of total RSI scores than PPI plus add- since the second week and until the end: $p<0.05$ at the second week; $p<0.01$ at the third week; and $p<0.05$

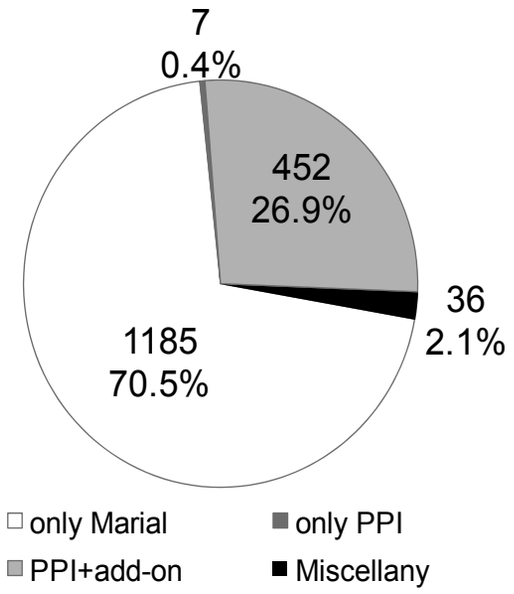

Fig. 1. *Distribution of the different treatments prescribed by the Otolaryngologists.*

at the fourth week. Noteworthy, both treatments reduced RSI scores below the cut-off (i.e. <13) since the second week. Moreover, Marial® induced a 74% reduction of RSI score, whereas PPI plus add-on a 70% reduction of RSI score ($p<0.0001$).

Fig. 4 reports the changes in RSI scores for each single symptom evaluated before and after the 4-week treatment with Marial®. All symptoms significantly diminished ($p=0.0001$ for all symptoms). Noteworthy to observe is that some symptoms disappeared, such as heartburning and dyspnoea.

Fig. 5 shows the changes in RSI scores for each single symptom evaluated before and after the 4-week treatment with PPI plus add-on. All symptoms significantly diminished ($p=0.0001$ for all symptoms). Noteworthy, some symptoms disappeared, such as heartburning difficulty to swallowing, and dyspnoea.

Fig. 6 shows the percentages of RSI reduction for each single symptom before and after a 4 week-

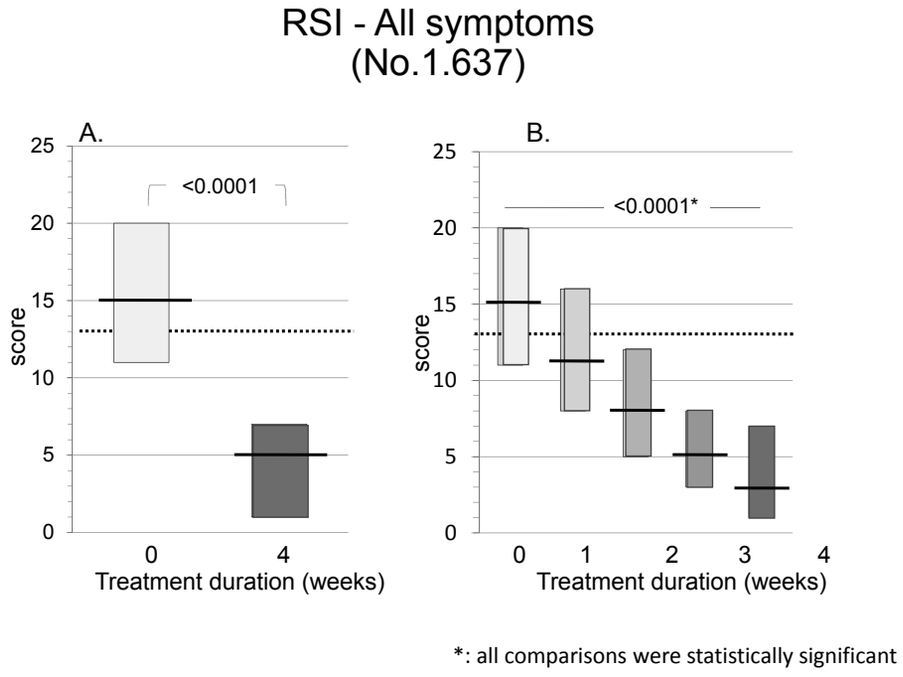

Fig. 2. *Total RSI value in all patients at baseline and after 4 weeks (i.e. end of the therapy)* ***(panel A)*** *and total RSI weekly trend over time* ***(panel B)***.

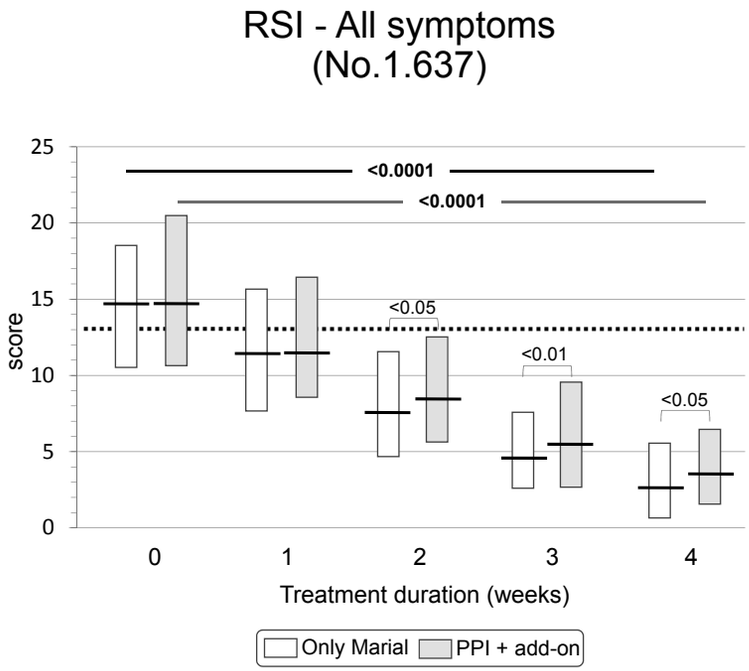

Fig. 3. *Trend of the total RSI values in patients treated with Marial® as monotherapy and with PPI plus add-on.*

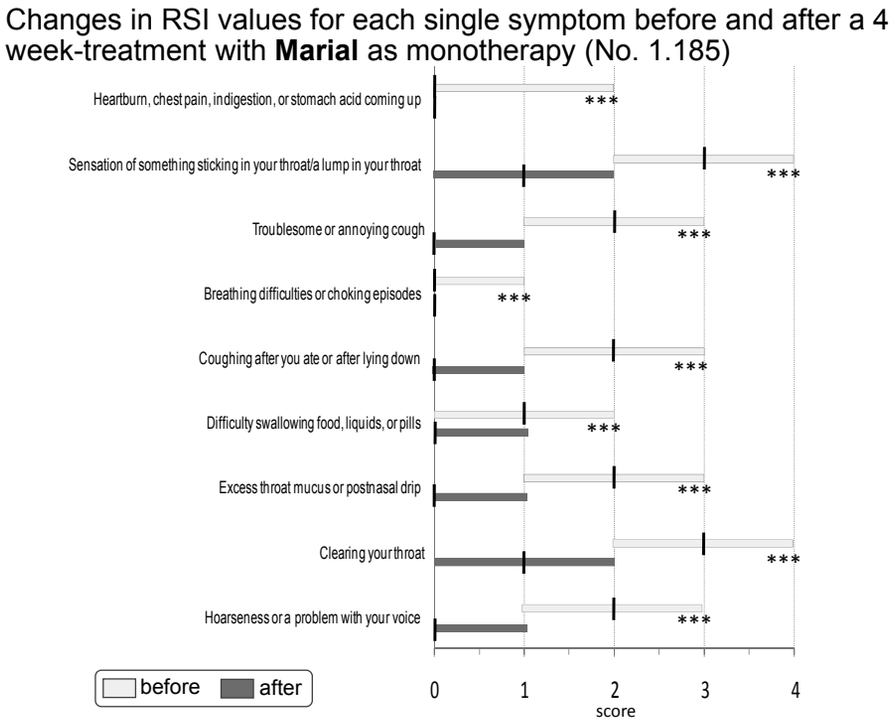

Fig. 4. *Changes in RSI scores for each single symptom evaluated before and after the 4-week treatment with Marial® alone.*

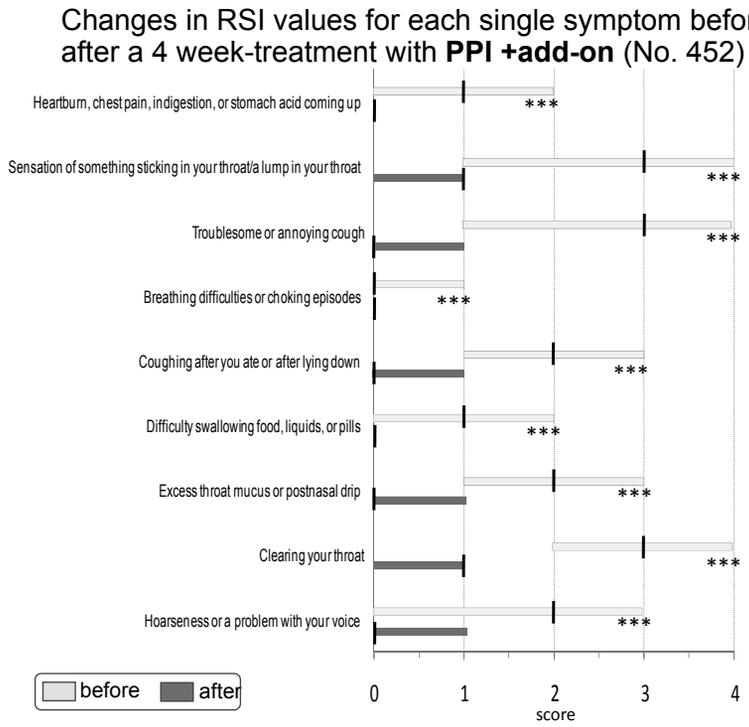

Fig. 5. *Changes in RSI scores for each single symptom evaluated before and after the 4-week treatment with PPI plus add-on.*

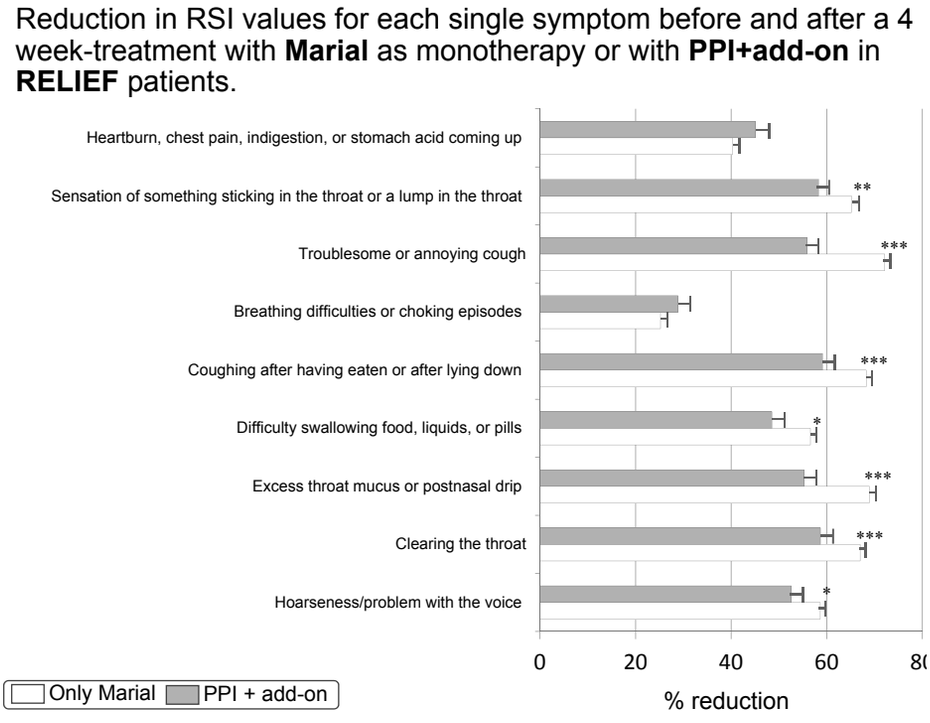

Fig. 6. *Percentages of RSI reduction for each single symptom in patients treated with Marial® as monotherapy and with PPI plus add-on.*

treatment with Marial® as monotherapy or with PPI in add-on. As compared to PPI in add-on, Marial® as monotherapy induced a statistically significant reduction in each single symptoms with the exception of breathing difficulties or choking episodes and heartburn, chest pain, indigestion, or stomach acid coming up.

DISCUSSION

Laryngopharyngeal Reflux constitutes a common disease, frequently underdiagnosed and mistreated. The diagnosis is based on patient's history and on a clinical ground. Validated method to assess the severity of signs and symptoms are very fruitful in clinical practice. In particular, the point of view of the LPR patient gained recognized respect and regard. The possibility of carefully measuring symptom severity by validated methods has allowed to obtain useful outcomes in clinical practice. In this regard, RSI is a validated psychometric questionnaire that is recommended both for LPR diagnostic work-up and evaluation of changes after treatments.

The launch in the Italian market of a new medical device (Marial®) represented an opportunity for LPR treatment. The novelty is the specific indication for LPR. Marial® is a combination of two substances: magnesium alginate and E-Gastryal® (a complex of phyto-polymers containing hyaluronic acid, hydrolysed keratin, Tara gum, and Xantana gum).

The present Italian survey aimed to evaluate the LPR management in clinical practice, mainly concerning the otolaryngologist clinic setting. In particular, the present analysis considered the LPR patient's perception of treatment changes using a validated method, such as the RSI score (14). Patients completed RSI questionnaires weekly during a 4-week treatment course. Therapeutic options were Marial® as monotherapy, or PPI plus add-on.

Globally, a significant reduction of symptom severity, measured by RSI, was achieved after both treatments. Interestingly, significant different change behaviour was evident among symptoms.

In particular, some symptoms disappeared, such as heartburning and dyspnoea. When comparing the two therapeutic options, it was demonstrated that Marial® induced a greater reduction of symptoms than PPI plus add-on since the second week. In particular, Marial® induced an 74% reduced of the RSI score, whereas PPI plus add-on gave a 70% reduction.

Even though the present survey should not be considered as a conventional trial, it permits to deduce some speculations. Marial® treatment was effective and rapid in relieving LPR complaints. Surprisingly, Marial® was more effective of PPI plus add-on. Another interesting issue is the rapidity of the therapeutic effect: since the second week.

Of course, the lack of a randomization, a double-blind design, a follow-up, and of a placebo group reduce the evidence-based scientific value of the current experience. Therefore, further studies should be conducted to address these unmet needs. However, the real-world setting, the large number of the recruited patients, and the use of a validate and consolidated instrument, i.e. the RSI questionnaire, have to be adequately considered. In particular, RSI assessment is clinically relevant as it expresses the point of view of the patients. This issue is very important as failing gold standard diagnostic criteria, the patient's perception of symptom severity change has a pragmatic value.

In conclusion, the present survey reported that a new medical device (Marial®) may be considered a valid option for the treatment of LPR.

REFERENCES

1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based con- sensus. Am J Gastroenterol 2006; 101:1900-20.
2. Bor S, Sarıtaş Yüksel E. How is the gastroesophageal reflux disease prevalence, incidence, and frequency of complications (stricture/esophagitis/Barrett's esophagus/carcinoma) in Turkey compared to other geographical regions globally? Turk J Gastroenterol 2017; 28(S1):S4-S9.
3. Fujiwara Y, Arakawa T. Epidemiology and clinical characteris- tics of GERD in the Japanese population.

J Gastroenterol 2009; 44:518-34.
4. Kellerman R, Kintanar T. Gastroesophageal Reflux Disease. Prim Care. 2017; 44:561-73.
5. Asaoka D, Nagahara A, Matsumoto K, Hojo M, Watanabe S. Current perspectives on reflux laryngitis. Clin J Gastroenterol 2014; 7:471-5.
6. Koufman JA. The otolaryngologic manifestations of gastro-esophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an exper- imental investigation of the role of acid and pepsin in the development of laryngeal injury. Laryngoscope 1991; 101:1-78.
7. Koufman J, Sataloff RT, Toohill R. Laryngopharyngeal reflux: consensus conference report. J Voice. 1996; 10:215-6.
8. Vaezi MF. Extraesophageal manifestations of gastroesophageal reflux disease. Clin Cornerstone 2003; 5:32-8.
9. Altman KW, Prufer N, Vaezi MF. The challenge of protocols for reflux disease: a review and development of a critical pathway. Otolaryngol Head Neck Surg 2011; 145:7-14.
10. Francis DO, Patel DA, Sharda R, Hovis K, Sathe N, Penson DF, et al. Patient-reported outcome measures related to laryngopharyngeal reflux: a systematic review of instrument development and validation. Otolaryngol Head Neck Surg 2016; 155:923-35.
11. Francis DO, Rymer JA, Slaughter JC. High economic burden of caring for patients with suspected extraesophageal reflux. Am J Gastroenterol 2013; 108:905-11.
12. Patrick DL, Burke LB, Powers JH, et al. Patient-reported outcomes to support medical product labeling claims: FDA perspective. Value Health 2007; 10(S2):125-37.
13. Regnault A, Hamel JF, Patrick DL. Pooling of cross-cultural PRO data in multinational clinical trials: how much can poor measurement affect statistical power? Quality Life Res 2015; 24:273-7.
14. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice 2002; 16:274-7.
15. Carrau RL, Khidr A, Gold KF. Validation of a quality-of-life instrument for laryngopharyngeal reflux. Arch Otolaryngol Head Neck Surg 2005; 131:315-20.
16. Sidhwa F, Moore A, Alligood E, Fisichella PM. Diagnosis and treatment of the extraesophageal manifestations of gastroesophageal reflux disease. Ann Surg 2017; 265:63-67.
17. Wright MR, Sharda R, Vaezi M. Unmet needs in treating laryngopharyngeal reflux disease: where do we go from here? Exp Rev Gastroenterol Hepatol 2016; 10:995-1004.
18. Kung YM, Hsu WH, Wu MC, Wang JW, Liu CJ, Su YC, et al. Recent advances in the pharmacological management of gastroesophageal reflux disease. Dig Dis Sci 2017; 62:3298-316.
19. McGlashan JA, Johnstone LM, Sykes J, Strugala V, Dettmar PW. The value of a liquid alginate suspension (Gaviscon Advance) in the management of laryngopharyngeal reflux. Eur Arch Otorhinolaryngol 2009; 266:243-51.
20. Woodland P, Lee C, Duraisamy Y, et al. Assessment and protection of esophageal mucosal integrity in patients with heartburn without esophagitis. Am J Gastroenterol 2013; 108:535-43.
21. Chiu CT, Hsu CM, Wang CC, et al. Randomised clinical trial: sodium alginate oral suspension is non-inferior to omeprazole in the treatment of patients with non-erosive gastroesophageal disease. Aliment Pharmacol Ther 2013; 38:1054-64.
22. Manabe N, Haruma K, Ito M, et al. Efficacy of adding sodium alginate to omeprazole in patients with nonerosive reflux dis- ease: a randomized clinical trial. Dis Esophagus 2012; 25:373-80.