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Minimum Effective Duration of Laryngopharyngeal Reflux Disease Treatment: A Prospective Study

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Abstract

Objective. To investigate the minimum therapeutic duration for patients with primary laryngopharyngeal reflux disease (LPRD) through the evaluation of symptom changes at multiple time points.

Study Design. Prospective uncontrolled.

Setting. University medical center.

Methods. Patients with LPRD at the 24-hour hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring were recruited from the European Reflux Clinic. Depending on the type of LPRD, patients were treated with a combination of proton-pump inhibitors, alginate, or magaldrate. Symptoms were evaluated with the reflux symptom score (RSS) at baseline and throughout treatment (1-, 3-, 6-, and 9-month posttreatment). The most appropriate therapeutic duration was determined using the RSS changes. Signs were evaluated with the reflux sign assessment.

Results. A total of 159 patients completed the study. The mean age was 49.9 ± 15.7 years. At 1-month posttreatment, 97 patients (61.0%) were considered as early responders to treatment, and the treatment was stopped for 52 patients (32.7%). Of the 62 early nonresponders, 34 patients (21.4%) reached responded to treatment after 3 to 9 months. The cumulative therapeutic success rate at 1-month posttreatment (61.0%) progressively increased to reach a range of 82.4% to 99.3% at 9-month posttreatment. The RSS mainly decreased in the first month of treatment in early responders. In early nonresponders, RSS progressively decreased throughout the 9-month treatment period. The baseline severity of RSS is a strong predictor of therapeutic response.

Conclusion. A therapeutic regimen of 1 month can be sufficient to treat one third of LPRD patients. The early nonresponders may require 3 to 9 months of treatment.

Keywords

duration, gastroesophageal, head neck surgery, laryngeal, laryngology, laryngopharyngeal, otolaryngology, reflux, signs, symptoms, treatment

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Laryngopharyngeal reflux disease (LPRD) is defined as a disease of the upper aerodigestive tract resulting from the direct and/or indirect effects of gastroduodenal content reflux, inducing morphological and/or neurological changes in the upper aerodigestive tract.[1] LPRD is associated with nonspecific laryngeal and extralaryngeal symptoms and findings that can be evaluated with validated patient-reported outcome questionnaires and clinical instruments.[1,2] The 24-hour hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMII-pH) is considered as the gold standard for the diagnosis and this approach can document the types of LPRD (acid, weakly acid, alkaline) indicating an appropriate therapeutic regimen.[3] It has long been suggested that the most appropriate duration of treatment ranges from 3 to 6 months, which was proposed as the overall duration for observing symptom relief in responder patients.[4,5] However, there are a few studies investigating the pre- to posttreatment dynamic of symptom evolution,[4,6] which makes the 3- to 6-month duration of LPRD treatment poorly evidence-based. Moreover, the recent observation of several clinical patterns of LPRD patients, including acute, recurrent, and chronic disease,[7] supports that the duration of treatment can be tailored according to the patient's responses and clinical patterns, leading to a personalized therapeutic approach.[8]

In the present study, the minimum therapeutic duration for patients with a LPRD at the 24-h HEMII-pH was investigated through the evaluation of symptoms changes

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at multiple time points. Precisely, this study aimed to provide data regarding the response rate of personalized treatments based on the HEMII-pH features.

Methods

Subjects and Setting

Patients with laryngopharyngeal symptoms and a diagnostic of LPRD at the 24-hour HEMII-pH were prospectively recruited from the European Reflux Clinic and Elsan Atlantic Polyclinic from September 2020 to January 2024. Patients were followed by the author of the study who is the primary practitioner of the European Reflux Clinic. The LPRD diagnosis was based on the detection of >1 pharyngeal acid, weakly acid or alkaline reflux event at the 24-hour HEMII-pH and it was consistent with the Dubai Consensus Criteria (IFOS—World Ear, Nose, and Throat Federation).[1] Patients with gastroesophageal reflux disease (GERD) symptoms or findings and aging individuals (>55 years) underwent gastrointestinal (GI) endoscopy. The following exclusion criteria were considered: active smoker with laryngopharyngitis, chronic alcohol consumption (>3 glasses/day), history of upper respiratory tract infection within the last month, neurological or psychiatric condition, head and neck malignancy, history of head and neck radiotherapy, uncontrolled asthma or inhaled corticosteroid-induced laryngitis, active seasonal allergies, history of fundoplication, or chronic consumption of antireflux medication at the time of the inclusion. Patients who did not adhere to the treatment were excluded. Patients had to consent to participate to the study. The ethics committee approved the protocol (IRB-CHU Saint-Pierre, Brussels, n°BE076201837630). The Strengthening the Reporting of Observational Studies in Epidemiology Statement was followed for the present manuscript.

HEMII-pH

The placement and characteristics of the HEMII-pH probe were previously described,[9] and adhere to the Dubai Consensus Criteria.[1] The catheter was composed of 8 impedance ring pairs and 2 pH electrodes (Versaflex Z®, LPR ZNID22+8R FGS 9000-17; Digitrapper pH-Z testing System; Medtronic). Six impedance segments were placed along the esophagus zones (Z1-Z6) below the cricopharyngeal sphincter. Two pharyngeal impedance segments were placed 1 and 2 cm above the cricopharyngeal sphincter. The LPR diagnosis was based on the detection of >1 pharyngeal acid, weakly acid, or alkaline reflux event at the 24-hour HEMII-pH. According to the Dubai Consensus Criteria, a pharyngeal reflux event was defined as an episode reaching the pharyngeal impedance sensors. The event was acid if its pH was ≤4.0. A nonacid reflux event consisted of an event with pH > 4.0.[1] Based on the number of acid and nonacid pharyngeal events, author defined an acid LPRD when the ratio of number of acid pharyngeal events/number of nonacid events was >2. LPRD was defined as alkaline when the ratio of number of acid events/number of nonacid events <0.5. The weakly acid LPRD consisted of a ratio ranging from 0.51 to 2.0. GERD diagnosis was based on the Lyon guidelines.[10] The patient was recommended to keep its normal diet during the 24-hour HEMII-pH, which was carried out off antireflux medication.

Symptoms, Findings and Types of Reflux

The symptoms were documented with the French version of the reflux symptom score (RSS), which rates the frequency and severity of otolaryngological, digestive, and respiratory symptoms.[11] The oral, pharyngeal, and laryngeal findings were evaluated in a blinded manner by the author of this study and a retired laryngologist with the full version of the reflux sign assessment (RSA).[12] Note that both laryngologists reported an adequate interclass coefficient ($r_s = 0.663$) regarding previous studies including some patients of the present study (RSA validation).[12] Because findings associated with LPRD take more time to change,[2] author did not evaluate the RSA at 1 month posttreatment.

The severity of LPRD was based on the symptom-related quality of life scores (RSS-QoL), which is a part of the RSS. RSS-QoL defines LPRD as mild (acute—RSS-QoL between 6 and 25), moderate (recurrent—RSS-QoL between 26 and 38), and severe (chronic—RSS-QoL > 38).[7] According to the therapeutic response, patients completed the RSS at baseline, 1-, 3-, 6-, or 9-month posttreatment. RSA was completed at baseline, 3-, 6-, and 9-month posttreatment.

Therapeutic Regimens

The therapeutic regimen strategies are summarized in **Figure 1**. The type of treatment was based on the HEMII-pH findings.[3] Patients with GERD findings or acid LPRD were treated with a proton-pump inhibitor (PPI) therapy or a combination of PPIs (pantoprazole, 40 MG/day), and postmeal alginate (Gaviscon® 3 times daily; Reckitt Benckiser). The treatment of patients with weakly acid LPRD consisted of a combination of PPI and postmeal alginate, while patients with an alkaline LPRD were treated with postmeal alginate or magaldrate (Riopan®, 3 times daily; Takeda). Note that the choice of alginate or magaldrate depended on the health care system and the availability of drugs in France and Belgium. Patients were instructed to adhere to an antireflux diet and lifestyle protocol.[13] The lifestyle protocol consisted of the reduction of stress and anxiety through personalized approaches (eg, sport, psychotherapy, yoga, meditation). The antireflux diet included the reduction of fat, low protein, high-released sugar foods and beverages, caffeine, spicy, raw vegetables, and alcohol. A list of recommended and discouraged foods and beverages is available in Supplemental

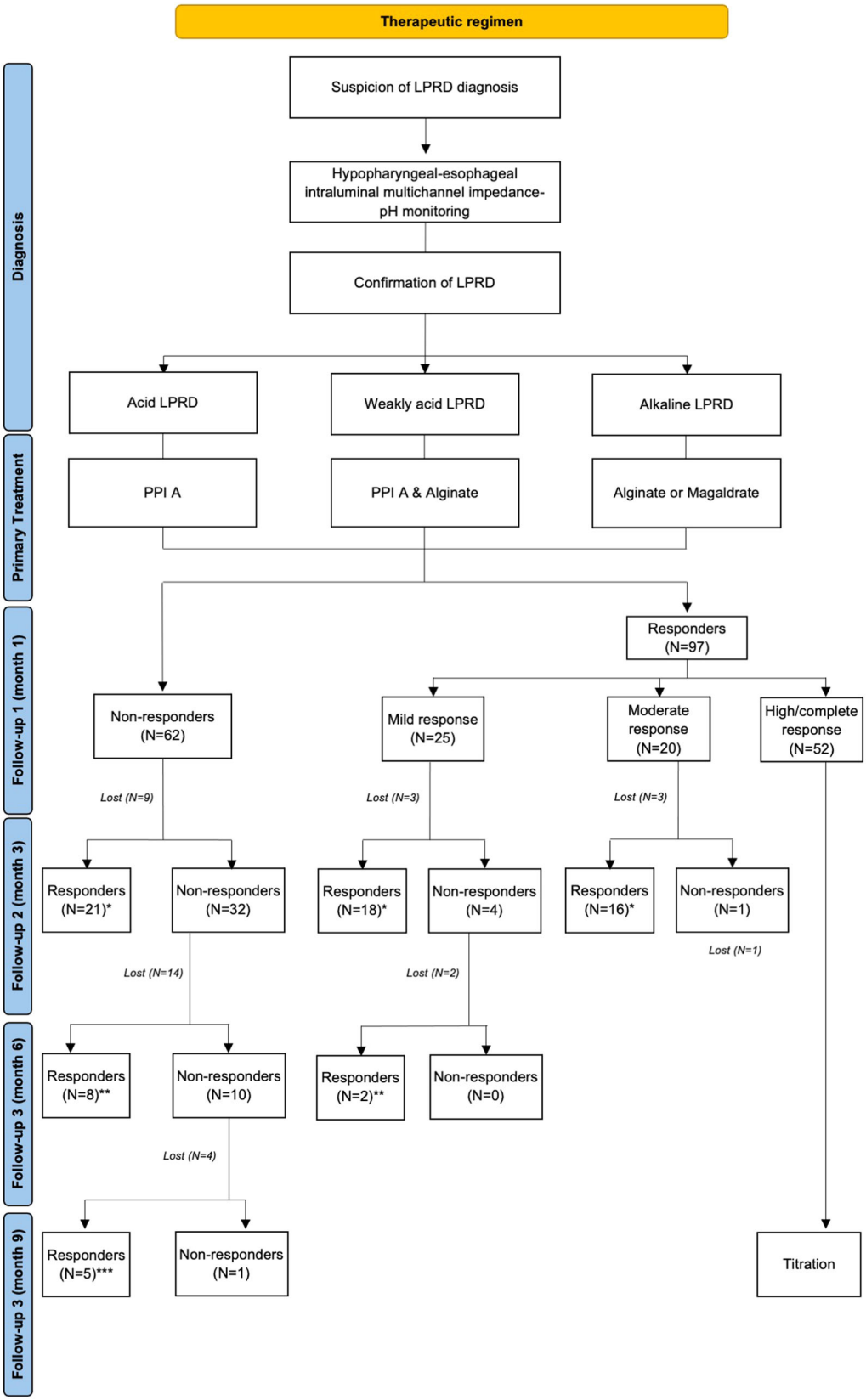

Figure 1. CONSORT chart flow. The treatment strategy was changed at each time point for nonresponders switching from some drug families to others. Note that at 1-month posttreatment, the treatment of patients with a mild-to-moderate response was progressively reduced (suppression of PPIs/progressive reduction of alginate/magaldrate), which was associated in some patients to additional improvements of symptoms or no change. The lack of additional symptom reduction after the first month of follow-up was expressed as a nonresponse in the figure (group of early responders). LPRD, laryngopharyngeal reflux disease; N, number; PPI, proton-pump inhibitors.

Appendices S1 and S2, available online. The duration of treatment depended on the patient response.

The primary treatment effectiveness was electronically evaluated after 1 month of treatment with the French version of the RSS.[11] An increase, unchanged, or a reduction of less than 20% in RSS was considered a nonresponse.[3] A decrease of 20.1% to 40% from the baseline RSS was considered a mild therapeutic response. A moderate therapeutic response consisted of a reduction in the baseline RSS between 40.1% to 60%. A reduction of 60.1% to 80% was considered a high response. The complete response was defined as a reduction of more than 80.1% in the baseline RSS.[3]

At 1-month posttreatment, the treatment of patients with a mild-to-moderate response was progressively reduced (progressive decrease of PPIs/progressive reduction of alginate/magaldrate). The treatment of patients with a high-to-complete response was stopped. The follow-up of patients with high-to-complete responses or with an RSS less than 13[11] was stopped after medication weaning. Weaned patients were instructed to continue the diet and lifestyle changes as much as possible. The treatment of nonresponder patients after the first therapeutic month was changed for 2 additional months, and they were re-evaluated every 3 months until reaching a significant clinical response (**Figure 1**). The medication changes consisted of PPI-drug changes or switching from alginate to magaldrate.

Statistical Methods

Statistical analyses were performed with the Statistical Package for the Social Sciences for Windows (SPSS version 30.0; IBM Corp). The pre- to posttreatment clinical changes (RSS, RSA) were evaluated with Wilcoxon Rank test. Univariate linear model was carried out to document predictors of therapeutic responses. The Spearman correlation coefficient was computed to test for the magnitude of the relationship between demographics, HEMII-pH, RSS and RSA outcomes. The outcome association was considered as low, moderate and strong for $k < 0.40$, 0.40 to 0.60, and $k > 0.60$, respectively. A level of significance of $P < .05$ was used.

Results

One hundred and fifty-nine patients completed the study. Forty-two (26.4%) patients were lost at the end of the 9-month follow-up, 35 (83.3%) being in the early nonresponder groups prior to be lost (**Figure 1**). There were 97 females (61.0%) and 62 males (39.0%). The mean age was 49.9 ± 15.7 years. The mean body mass index was 24.5 ± 5.4. Demographics and clinical features are reported in **Table 1**. The cohort included 67 (42.1%), 45 (28.3%), and 47 (29.6%) patients with mild, moderate, and severe LPRD,[7] respectively. One hundred and ten patients underwent a GI endoscopy, which was unremarkable in 15.5% of cases (**Table 1**). Lower esophageal sphincter insufficiency and hiatal hernia were found in 51 (46.4%) and 31 (28.2%) patients, respectively. Among the 51 (46.4%) patients with esophagitis, 3 had Barrett metaplasia (2.7%). The 24-hour HEMII-pH findings are described in **Table 1**. Most pharyngeal reflux events occurred daytime and upright. There were 59 (37.1%) patients with both LPRD and GERD (**Table 1**). Demographics and clinical features are reported in **Table 1**.

Table 1. Epidemiological and Clinical Features of Patients

Characteristics	Patients (N = 159)
Mean age (range, y)	49.9 ± 15.7
Body mass index (mean, SD)	24.5 ± 5.4
Gender (N, %)	
Male	62 (39.0)
Female	97 (61.0)
Severity of reflux (RSS-QoL)	
Mild reflux (<26)	67 (42.1)
Moderate reflux (26-38)	45 (28.3)
Severe reflux (>38)	47 (29.6)
Gastrointestinal endoscopy	N = 110
Normal	17 (15.5)
Esophagitis	51 (46.4)
Hiatal hernia	31 (28.2)
LES insufficiency	51 (46.4)
Gastritis	44 (40.0)
Barrett metaplasia	3 (2.7)
Helicobacter pylori infection	9 (8.2)
HEMII-pH feature (mean, SD)	
Pharyngeal events	
Pharyngeal acid reflux events	15.9 ± 16.6
Pharyngeal nonacid reflux events	18.3 ± 21.9
Total number of pharyngeal events	34.4 ± 24.9
Position events	
Pharyngeal event upright	28.6 ± 22.7
Pharyngeal event supine	5.2 ± 8.7
GERD	
Number of patients (%)	59 (37.1)
Percentage of time with distal pH<4	10.3 ± 18.2

Results are described as N and percentages (%) or mean (SD).
Abbreviations: GERD, gastroesophageal reflux disease; HEMII-pH, hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring; LES, lower esophageal sphincter; RSS-QoL, reflux symptom score quality of life; SD, standard deviation.

Therapeutic Success Rates

The therapeutic response rates at 1-, 3-, 6-, and 9-month posttreatment are reported in **Figure 1**. Ninety-seven patients (61.0%) reported significant RSS reduction (>20% reduction) after 1 month and were considered early responders. There were 43 mild (44.3%), 26 moderate (26.8%), and 28 severe (28.9%) LPRD in the early responder group. Sixty-two patients (39.0%) had nonsignificant RSS reduction and were considered as

early nonresponders. There were 24 mild (39.7%), 19 moderate (30.6%), and 19 severe (30.6%) LPRD in the early nonresponder group (Supplemental Appendix S3, available online).

Among early responder patients, the treatment was stopped for 52 patients (53.6%) with high-to-complete responses, which consisted of 32.7% of the entire cohort. Among the 1-month early nonresponder patients (N = 62), 21 patients (33.9%) responded to treatment at 3 months posttreatment, while 32 patients (51.6%) were still nonresponders. Nine patients (14.5%) were lost of follow-up from the first to the third month posttreatment (**Figure 1**). Among the 32 nonresponder patients at 3-month posttreatment, 8 patients (25%) reported clinical response at 6-month posttreatment and 10 patients were still nonresponders (31.3%). Of the 10 nonresponders at 6-month posttreatment, 5 individuals reached clinical response at 9-month posttreatment (**Figure 1**).

Considering the patients who were lost of follow-up as undetermined responder patients, the 3-month therapeutic success rate could range from 74.2% to 78.7%. The 6-month cumulative therapeutic success rate could range from 79.2% to 92.6%. The 9-month cumulative therapeutic success rate could range from 82.4% to 99.3% (**Figure 1**). Note that there were no significant differences between responder and nonresponder groups regarding the types of LPRD (acid, weakly acid, and alkaline).

Evolution of Symptoms and Findings

The symptoms and findings of early responder patients are reported in **Table 2** and **Figure 2**. RSS significantly decreased from baseline to 1-, 3-, 6-, and 9-month posttreatment. Pharyngeal, laryngeal, and total score of RSA significantly decreased from baseline to 3-month posttreatment, while all RSA items and total score significantly decreased from baseline to 6- and 9-month posttreatment. The evolution of signs and symptoms of early nonresponder patients is shown in **Table 3**. The RSS reached significant reduction after 6- and 9-month posttreatment. RSA significantly decreased from baseline to 3- and 6-month posttreatment.

Figure 2 describes the evolution of RSS and RSA items between time-point of assessment. The changes in RSS and RSA from 1- to 3-month, 3- to 6-month, and 6- to 9-month posttreatment substantially differed between groups. In the early responder group, the RSS did not change from 1- to 9-month posttreatment, while the pharyngeal, laryngeal, and total scores of RSA continued to decrease from 3- to 6-month posttreatment. In the early nonresponder group, the RSS significantly decreased from 1- to 3-month, and 3- to 6-month posttreatment, respectively (**Figure 2**).

Study of Associations

There were low but significant associations between the number of nonacid pharyngeal reflux events and the 1-month ($r_s = 0.177$; $P = .046$), and 6-month posttreatment RSS ($r_s = 0.257$; $P = .044$), meaning that nonacid pharyngeal events could predict the severity of 1- and 6-month RSS. The baseline RSS was a strong and significant predictor of the 1- ($r_s = 0.615$; $P = .001$), 3- ($r_s = 0.544$, $P = .001$), 6- ($r_s = 0.0498$; $P = .001$), and 9-month RSS ($r_s = 0.453$; $P = .020$), meaning that patients with a high RSS at baseline kept a high RSS throughout treatment. There was no significant association between symptoms (RSS) and signs (RSA).

Discussion

A recent otolaryngologist survey reported that most of the practitioners recommended a minimum therapeutic duration of 3 months for LPRD.[14] In the same vein, most clinical studies or reviews dedicated to the treatment of LPRD suggested a minimum LPRD therapeutic duration ranging from 3 to 6 months.[2,4,5,15] To date, there are a few studies reporting data on the dynamic of symptom evolution in the first weeks of treatment,[6] making it difficult to establish a minimum therapeutic duration.

Table 2. Evolutions of Symptoms and Findings in Early Responder Patients

Symptom scores	Baseline	1 mo	*P* value	3 mo	*P* value	6 mo	*P* value	9 mo	*P* value
Otolaryngological reflux symptom score	51.9 ± 33.6	25.9 ± 24.1	.001	23.1 ± 26.5	.001	24.2 ± 33.7	.001	22.3 ± 18.9	.0012
Digestive reflux symptom score	42.6 ± 32.5	16.5 ± 15.4	.001	18.3 ± 20.2	.001	24.2 ± 36.7	.001	18.9 ± 21.0	.004
Respiratory reflux symptom score	17.2 ± 20.7	6.8 ± 10.2	.001	6.5 ± 12.5	.001	7.5 ± 13.8	.001	11.8 ± 22.5	.012
Reflux symptom score—QoL	30.7 ± 17.3	17.9 ± 12.0	.001	17.8 ± 12.8	.001	17.0 ± 17.4	.001	18.3 ± 12.2	.005
Reflux symptom score	111.8 ± 62.7	49.2 ± 38.5	.001	48.0 ± 45.3	.001	55.9 ± 75.2	.001	53.1 ± 45.1	.002
Sign scores									
Oral cavity subscore	5.5 ± 2.4	-	-	5.1 ± 2.2	NS	4.4 ± 1.9	.015	3.8 ± 2.2	.046
Pharyngeal cavity subscore	10.3 ± 4.0	-	-	7.7 ± 3.8	.001	6.7 ± 4.2	.001	7.2 ± 5.5	.003
Laryngeal subscore	13.0 ± 5.7	-	-	8.5 ± 5.6	.001	6.6 ± 5.6	.001	6.8 ± 4.7	.017
RSA total score	27.9 ± 8.0	-	-	21.1 ± 8.7	.001	17.9 ± 8.5	.001	18.3 ± 7.4	.010

The data are related to the 62 early nonresponders.
Abbreviations: mo, month; NS, nonsignificant; QoL, quality of life; RSA, reflux sign assessment.

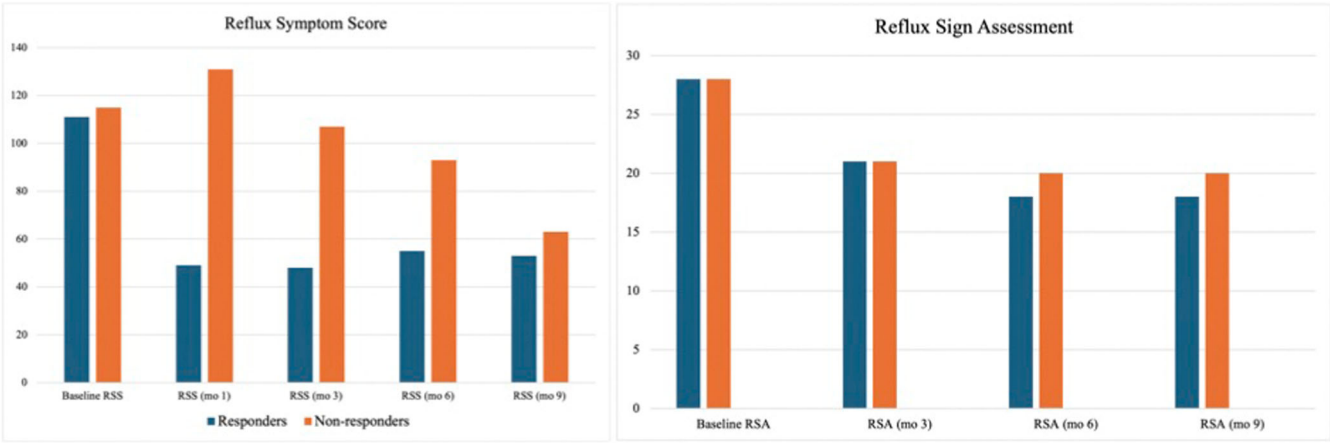

Figure 2. Evolutions of symptoms and findings in early responder and nonresponder patients. mo, month; RSA, reflux sign assessment; RSS, reflux symptom score.

Table 3. Evolutions of Symptoms and Findings in Early Nonresponder Patients

Symptom scores	Baseline	1 mo	*P* value	3 mo	*P* value	6 mo	*P* value	9 mo	*P* value
Otolaryngological reflux symptom score	58.1 ± 43.7	67.5 ± 41.5	NS	54.4 ± 40.5	NS	50.4 ± 49.1	NS	36.0 ± 24.0	.002
Digestive reflux symptom score	36.9 ± 34.9	40.6 ± 37.5	NS	35.8 ± 40.8	NS	31.2 ± 35.9	NS	16.8 ± 20.1	.016
Respiratory reflux symptom score	20.1 ± 22.1	23.3 ± 25.5	NS	17.1 ± 22.1	NS	11.6 ± 20.3	.001	10.4 ± 12.4	NS
Reflux symptom score—QoL	33.4 ± 19.2	35.8 ± 19.8	NS	29.9 ± 20.2	.025	26.9 ± 20.4	.015	21.5 ± 13.0	.016
Reflux symptom score	115.1 ± 79.6	131.3 ± 86.7	NS	107.2 ± 88.5	NS	93.2 ± 95.6	.030	63.2 ± 41.4	.006
Sign scores									
Oral cavity subscore	5.5 ± 2.1	-	-	4.6 ± 2.3	NS	4.9 ± 2.5	NS	4.3 ± 2.8	NS
Pharyngeal cavity subscore	10.2 ± 4.7	-	-	7.4 ± 4.0	.002	8.9 ± 4.7	NS	6.9 ± 4.4	NS
Laryngeal subscore	12.9 ± 5.9	-	-	8.8 ± 4.8	.001	6.8 ± 5.8	.003	8.3 ± 5.8	.022
RSA total score	28.1 ± 9.4	-	-	20.6 ± 7.5	.001	20.5 ± 8.9	.024	19.5 ± 8.1	NS

The data are related to the 62 early nonresponders.
Abbreviations: mo, month; NS, nonsignificant; RSA, reflux sign assessment; QoL, quality of life.

The findings of the present study support that one-third of patients can reach total symptom relief after 1 month of personalized treatment, while up to 40% with partial symptom relief required 3-, 6-, or ≥9 months of treatment. In this last group, some patients had a chronic course of the disease, which can indicate the need for long-term medication. The studies reporting at least 2-time point data of symptom changes with patient-reported outcome questionnaires in the first months of treatment are summarized in **Table 4**.[4,6,16-23]

In 2006, Reichel et al reported a significant reduction of the reflux symptom index (RSI) in suspected LPRD patients after 6 and 12 weeks of empirical PPI therapy consisting of twice daily esomeprazole (20 mg) (**Table 4**).[16] The achievement of a significant therapeutic response at the 6-week posttreatment was similarly reported by Lam et al in a study including 82 suspected LPRD patients who were treated with rabeprazole (20 mg twice daily).[17] In this study, the baseline RSI (14.5) significantly reduced after 6 weeks of treatment (11.6) but did not significantly change from the 6-week (RSI = 11.7) to 12- and 18-week (RSI = 12.3) posttreatment. In the same vein, Chung et al investigated the RSI changes after 6 and 12 weeks of lansoprazole (30 mg/day) in suspected LPRD patients.[18] The authors did not report an RSI change after 1 month of PPIs (RSI = 19.2-16.6). At the 2-month posttreatment, the RSI was significantly reduced (RSI = 13.7), which suggested that the minimum duration of treatment could be up to 1 month.[18] The lack of improvement after 1 month was not corroborated in the study of Chun et al and Park et al who both reported a significant RSI reduction after 1 month and 12 weeks of PPIs.[19,20] Belafsky et al reported that most symptom changes occurred within the 2 first months of treatment.[4] Bhardwaj et al similarly reported that 65.2% of patients with suspected LPRD had partial relief of symptoms after 1 month of treatment,[24] which corroborates our results suggesting a 61.0% response rate at 1 month posttreatment. The early response rates found in our study and the study of Bhardwaj et al are higher compared to those found in a recent PPI-therapy-based study where authors found 19.9% RSI improvement at the 6-week posttreatment.[25] The dynamics of symptom and sign changes have been studied in detail by

Table 4. Studies Investigating the Symptom Changes Throughout Treatment

References	Patients	N	Age, y	PROM	Baseline	2 wk	1 mo	6 wk	2 mo	3 mo	4 mo	6 mo	9 mo	Treatment, mg
Belafsky et al[4]	Acid LPR	39	50.0	RSI	19.3	-	-	-	13.9	-	13.1	12.2	-	PPI 30-40
Reichel et al[16]	Suspected LPR	30	48.7	RSI	21.8	-	-	11.9	-	7.5	-	-	-	Esomeprazole 40
Jin et al[6]	Acid LPR	40	53.7	RSI	8.6	5.3	3.2	-	2.2	1.2	0.9	-	-	Lansoprazole 30 + levosulpride 75
Lam et al[17]	Suspected LPR	42	46.8	RSI	14.5	-	-	11.6	-	11.7	13.6	-	-	Rabeprazole 40
Masaany, et al[22]	Suspected LPR	47	18-60	RSI	19.4	-	-	-	10.9	6.8	4.3	-	-	Pantoprazole 40
Chung et al[18]	Suspected LPR	22	48.0	RSI	19.2	-	16.6	-	13.7	-	-	-	-	Lansoprazole 30
Park et al[20]	Suspected LPR	50	55.0	RSI	18.7	-	13.8	-	12.2	10.7	-	-	-	Omeprazole 40
Chun et al[19]	Suspected LPR	32	51.7	RSI	20.7	-	-	12.3	-	8.3	-	-	-	Lansoprazole 30
Ozturan et al[21]	Suspected LPR	65	18-60	RSI	26.7	-	17.8	-	11.0	-	-	-	-	Esomeprazole 40
Joshi et al[23]	Suspected LPR	100	41.5	RSI	11.8	-	9.1	-	5.6	3.8	-	2.0	-	Omeprazole 40

Studies reporting several time-point symptom assessments with validated patient-reported outcome questionnaires were summarized.
Abbreviations: LPR, laryngopharyngeal reflux; mo, month; PPI, proton-pump inhibitors; PROM, patient-reported outcome questionnaire; RSI, reflux symptom index; wk, week; y, year.

Jin et al every 2 weeks after the start of the PPI therapy (lansoprazole 30 mg/day and levosulpride 25 mg, 3/day) in 40 patients with acid LPRD at the dual-probe pH-monitoring.[6] Interestingly, Jin et al showed a significant reduction in RSI at 2-, 4-, 8-, and 12-week posttreatment (**Table 4**).[6] This study is important because the authors highlighted that the highest RSI score reduction occurred within the first 4 to 8 weeks of treatment, which corroborates our observations and those of other studies. Despite a significant reduction in symptoms in the first 4 to 8 weeks of treatment, none of these authors have tried to stop or reduce the medication doses at that time nor followed these patients up to assess their symptom response/relief. Moreover, the included patients had no confirmed LPRD,[16-20] or acid LPRD,[6] and were followed by an RSI that does not include all LPRD-related symptoms, which may bias the comparison with our study. Moreover, the use of PPI therapy in suspected LPRD may not guarantee an adequate therapeutic response according to the highest proportion of patients with weakly acid or alkaline LPRD compared to acid LPRD.[26,27]

The observation of the present study opens new findings in LPRD management. Indeed, LPRD is associated with a high cost burden in the United States[28] with a significant part of the cost dedicated to 3- to 6-month empirical therapeutic trials, which can be ineffective in more than 40% of cases.[29] The use of a degressive therapeutic regimen considering a first evaluation of symptom changes within the 4- to 8-week posttreatment could reduce the cost burden and the potential adverse events associated with PPI therapy.[30] In addition, a shortened therapeutic duration could be a response to the lack of therapeutic compliance found in LPRD patients.[31]

However, despite an adequate and adapted therapeutic duration, the present study highlights that a significant proportion of patients do not rapidly reach partial or total symptom relief; some of them suffer from a chronic course of the disease. The etiology of a chronic course remains unknown. Autonomic nerve dysfunction,[32] and modifications of the upper aerodigestive tract microbiome were suspected as contributing factors but there are no well-conducted transversal studies exploring these hypotheses. According to our observation of a potential association between the baseline RSS and the therapeutic response (posttreatment RSS), patients with a high baseline RSS could benefit from a longer and more aggressive therapy than those with low-to-moderate RSS. The use of the RSS-QoL score as a predictor of therapeutic treatment,[13] could be an issue for further studies investigating predictive outcomes.

The main strengths of the study include the high number of LPRD patients diagnosed with the 24-hour HEMII-pH and the consideration of the full version of the RSS that includes most LPRD symptoms. The determination of a minimum therapeutic duration for LPRD patients and the proportion of responders at 1, 3, 6, or 9 months of treatment are additional strengths that were not fully

investigated within a single trial. Indeed, most authors reported statistics of patient-reported outcome questionnaires improvement without providing details about the responder versus nonresponder evolution. The lack of additional symptom evaluations at 2 and 8 weeks of treatment is the primary limitation of the study. These could lead to more precise data for establishing the minimum therapeutic duration but in practice, additional assessments were difficult to achieve full adherence from patients to the protocol. The moderate number of patients who were lost to follow-up is an additional limitation leading to inability to establish a more accurate therapeutic success rate. In our experience, they included patients without symptom changes, or by contrast, patients with symptom relief and no intention to adhere to the last consultation follow-up. Finally, some patients reported fluctuating symptoms over time. Thus, they can have first improvements followed by a recurrence of symptoms. This pattern was poorly investigated, and the clinical fluctuations can bias the present analysis.

Conclusion

A therapeutic regimen of 1 month can be sufficient to treat one third of LPRD patients. The nonresponders may require 3 to 9 months of treatment. Most patients can be weaned from antireflux medication. The consideration of a limited treatment duration can have a significant impact on the cost burden related to the LPRD management.

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Author Contributions

Jerome R. Lechien, design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosures

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Supplemental Material

Additional supporting information is available in the online version of the article.

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