

Effectiveness of Changing Drug Classes in Patients With Refractory Laryngopharyngeal Reflux Disease

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Abstract

Objective. To investigate the effectiveness of drug class changes in patients with refractory laryngopharyngeal reflux disease (LPRD).

Study Design. Retrospective case series with prospective data.

Setting. Multicenter study.

Methods. The data of patients treated for a refractory LPRD from September 2017 to December 2023 were collected. The effectiveness of drug class changes was assessed through the reflux symptom score (RSS) change. Signs were evaluated with the Reflux Sign Assessment. The RSS reduction was used to categorize the therapeutic responses as mild (20%–40% RSS reduction), moderate (40.1%–60% RSS reduction), high (60.1%–80%), and complete (>80%).

Results. Among the 334 medical records, 74 (22.2%) patients had refractory LPRD defined as no RSS change in the pre- to 3-month posttreatment. The mean age was 52.6 ± 15.5 years. Changing drug class was associated with significant 3- to 6-month posttreatment reductions of RSS and RSA. Thirty patients (39%) did not experience symptom reduction after changing drugs. Changing alginate to magaldrate and magaldrate to alginate was associated with the highest responder rate (76.9%). Changing PPI and alginate/magaldrate molecules led to a response rate of 62.5%. In patients initially treated with a combination of PPI and alginate or magaldrate, changing PPI without changing alginate/magaldrate led to a 37.5% response rate. The baseline RSS was predictive of the 3- and 6-month RSS (therapeutic response).

Conclusion. Changing drug class, especially alginate-to-magaldrate, may be an effective therapeutic approach for patients with a refractory LPRD.

Keywords

change, gastroesophageal, head neck surgery, laryngology, laryngopharyngeal, medication, otolaryngology, refractory, reflux

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Laryngopharyngeal reflux disease (LPRD) symptoms are prevalent in otolaryngology head and neck surgery, accounting for 10% to 30% of outpatients in Western countries.^{1,2} The treatment of LPRD is challenging due to the heterogeneous nature of symptom pathology, lack of international therapeutic consensus, and variable response to therapies.^{2,3} To date, the superiority of proton pump inhibitors (PPIs) over placebo has still not been demonstrated.⁴ PPI therapy is associated with a mean therapeutic response rate ranging from 17% to 87% of cases.⁵ The low efficacy of PPI therapy may be related to the weakly acidic or alkaline nature of most LPRD measured at the hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMII-pH),^{6,7} which may support the use of alginate or magaldrate (antacids) drugs in the empirical treatment of LPRD.^{8,9} To date, most practitioners increase PPI doses in patients without symptom reduction. They authors apply the same strategies than those for the refractory gastroesophageal reflux disease (GERD).¹⁰ In otolaryngology head and neck surgery, there is no clinical study investigating the effectiveness of drug class changes in patients with refractory LPRD. However, changing drug class could be an interesting therapeutic approach regarding the variability of reflux events at the HEMII-pH, and the spectrum of efficacy of

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the several available drugs (eg, alginate, magaldrate, PPIs) for GERD and LPRD.^{3,11}

In the present study, we retrospectively investigated the effectiveness of drug class changes in LPRD patients who were prospectively treated in 3 European hospitals.

Methods

Setting and Patients

This study was a retrospective case series with prospective data of patients who were treated for a refractory LPRD from September 2017 to December 2023 in 3 European hospitals (Poitiers Elsan Polyclinic; Foch Hospital of Suresnes; and CHU Saint-Pierre of Brussels). Only patients with a refractory LPRD and complete clinical and therapeutic data follow-up from baseline to 3- and 6-month posttreatment were included.

The LPRD diagnosis was based on the Dubai criteria¹² considering the presence of more than 1 pharyngeal reflux event at the 24-hour HEMII-pH (Versaflex Z[®], Digitrapper pH-Z testing System; Medtronic) off acid suppressive medication for 2 weeks.

The following criteria were considered to indicate upper gastrointestinal (GI) endoscopy: gastroesophageal reflux disease (GERD)-related symptoms; undetermined weight loss; hematemesis; and history of Barrett's metaplasia.¹² The following exclusion criteria were considered: upper respiratory tract infection within the last month, use of anti-reflux therapy, neurological or psychiatric diseases, head and neck malignancy, history of head and neck radiotherapy, active seasonal allergies, intake of inhaled corticosteroids, and asthma. Moreover, patients who did not adhere to the treatments (diet and medications) were excluded from this analysis. The local IRB approved the study protocol (CHU Saint-Pierre, n°BE076201837630; Brussels).

Hypopharyngeal-Esophageal Impedance-pH Testing and Definition of LPRD

The HEMII-pH catheter was composed of 6 esophageal and 2 pharyngeal impedance ring pairs and 2 pH electrodes (Versaflex Z[®], LPR ZNID22 + 8 R FGS 9000-17; Digitrapper pH-Z testing System; Medtronic). The catheter model used was introduced transnasally and chosen based on the esophageal length. Six impedance segments were placed along the esophagus zones (Z1 to Z6) below the upper esophageal sphincter (UES). Two additional impedance segments were placed 1 and 2 cm above the UES in the hypopharynx. The 2 pH electrodes were placed 5 cm above the lower esophageal sphincter (LES) and 1 to 2 cm above the cricopharyngeal sphincter. The catheter was placed in the morning before breakfast (8:00 a.m.).

A pharyngeal reflux event was defined as an episode that reached 2 pharyngeal impedance sensors.¹² The LPRD diagnosis was considered for patients with

>1 pharyngeal reflux event.^{12,13} An acid pharyngeal event was defined as an episode with pH ≤ 4.0.¹⁴ Nonacid reflux consisted of an episode with pH > 4.0. Consistent with previous publications,¹⁴ LPRD was defined as acid when the ratio of the number of pharyngeal acid reflux episodes to the number of nonacid reflux episodes was >2. LPRD was defined as nonacid when the ratio of the number of acid reflux episodes to the number of nonacid reflux episodes < 0.5. Weakly acidic reflux consisted of a ratio ranging from 0.51 to 2.0. GERD was defined according to the Lyon consensus.¹⁵

Clinical Assessment

Symptoms were assessed with the French version of the Reflux Symptom Score (RSS),¹⁶ which evaluates the frequency and severity of otolaryngological, digestive, and respiratory symptoms. The impact of symptoms on quality of life (QoL) was assessed with the RSS-QoL. The RSS-QoL was used to define the severity of LPRD, considering mild (acute) LPRD for a RSS-QoL between 6 and 25, moderate (recurrent) LPRD for patients with RSS-QoL between 26 and 38, and severe (chronic) LPRD for patients with RSS-QoL > 38.¹⁷ The oral, laryngeal, and pharyngeal findings were assessed with Reflux Sign Assessment (RSA).¹⁸ The RSA findings were evaluated by 2 laryngologists in a semi-blind manner. Practitioners did not know the patient's symptoms at the time of the videolaryngostroboscopic examination. RSS and RSA were assessed at baseline, 3- and 6-month posttreatment.

Primary and Secondary Treatments

Based on the HEMII-pH findings, patients were treated with a standardized anti-reflux diet,¹⁹ and a combination of PPIs (40 mg once in the morning), postmeal alginate (Gaviscon Advance[®], Reckitt Benckiser, Slough, UK; 3/d) or magaldrate (Riopan[®], 3/d; Takeda) for 3 months (**Figure 1**).¹⁴ Patients with acid pharyngeal reflux events at the HEMII-pH (acid LPRD) were treated with PPI only. Patients with weakly acidic LPRD received a combination of PPI and alginate, while patients with alkaline LPRD were treated with alginate or magaldrate only. Magaldrate is an antacid that is recognized to have pepsin/bile acid chelator role, which is not the primary mechanism of alginate, which forms a raft over the stomach content. The choice of alginate or magaldrate for alkaline LPRD depended on the healthcare system. In France, magaldrate is not commonly available in the reimbursed medication list, making the prescription of alginate easier. In Belgium, both alginate and magaldrate are similarly available for patients.

The therapeutic response was evaluated through the evolution of the RSS from baseline to 3-month posttreatment, and from 3- to 6-month posttreatment. Patients with a refractory LPRD (nonresponders) were individuals with increased, unchanged, or 1% to 20% reduced RSS after the 3-month therapeutic regimen.¹⁴ A reduction of

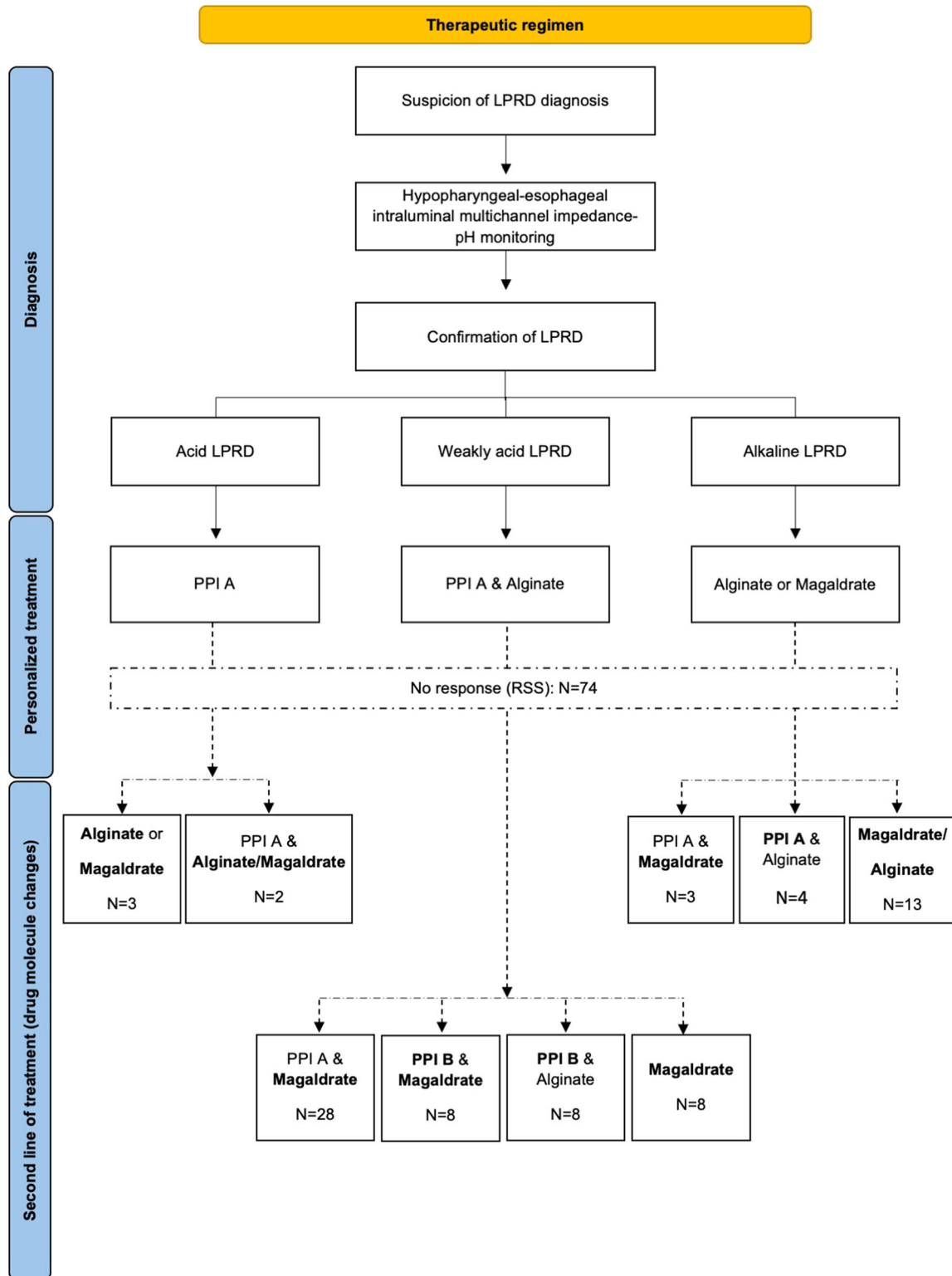


Figure 1. Chart flow. The primary medication was selected regarding the type of LPRD (acid/weakly acid/alkaline). Magaldrate was preferred to alginate for alkaline LPRD but it was available only in Belgium). In bold, the changes. LPRD, laryngopharyngeal reflux disease; N, number; PPI, proton pump inhibitor(s); RSS, reflux symptom score.

20.1% to 40% in the RSS was defined as a mild therapeutic response. A moderate therapeutic response was defined when the RSS was reduced by 40.1% to 60% of its pre-therapeutic value. A reduction of 60.1% to 80%

was considered a high response, while a reduction of more than 80.1% was defined as a complete response.¹⁴

The change of medication was based on the following concepts: (1) alginate or magaldrate has been added in

patients unsuccessfully treated with PPI therapy only (acid LPRD) because they were suspected to have weakly acidic LPRD; (2) patients unsuccessfully treated with alginate received magaldrate and vice versa given the different mechanisms of both drugs; and (3) the PPI was changed in patients unsuccessfully treated with PPI and alginate/magaldrate if patients had persisting GERD symptoms despite PPI.

Statistical Methods

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS version 30.0; IBM Corp.). The pretreatment to posttreatment evolution of RSS and RSA was assessed with the Wilcoxon signed-rank test. The predictive value of demographic and clinical outcomes on the therapeutic response was evaluated with the Spearman correlation coefficient and the Chi-square according to the type of data. A level of significance of $P < .05$ was used.

Results

Among the 334 patients who were prospectively followed, 74 (22.2%) did not respond to the baseline 3-month therapeutic regimen and were considered as suffering from refractory LPRD.¹⁴ Three patients reported 2 consecutive therapeutic failures. There were 38 (49.4%) males and 39 (50.6%) females, respectively. The mean age was 52.6 ± 15.5 years old. The mean BMI was 24.3 ± 4.2 . The GI endoscopy features are described in **Table 1**. Sixteen patients had unremarkable GI endoscopy. The cohort included 17 (23.0%) patients with mild LPR, 32 (43.2%) patients with moderate LPR, and 25 (33.8%) patients with severe LPR, respectively. The baseline unsuccessful therapeutic regimens included the combination of PPI with alginate or magaldrate ($N = 52$), alginate or magaldrate ($N = 20$), and PPI ($N = 5$; **Figure 1** and **Table 2**).

As expected, the RSS did not significantly change from pre- to 3-month posttreatment (**Table 3**). The laryngeal and total scores of reflux sign assessment significantly improved from baseline to 3-month posttreatment (**Table 4**). Changing medication was associated with a significant decrease of RSS from 3- to 6-month posttreatment (**Table 3**). The laryngeal and total RSA scores continued to decrease from 3- to 6-month posttreatment (**Table 4**). The several drug changes and responses are summarized in **Table 2**. In the group of patients initially treated with a combination of PPI and alginate or magaldrate, changing PPI without changing alginate/magaldrate led to a 37.5% response rate. Changing alginate/magaldrate while keeping PPI was associated with a 67.9% response rate (**Table 2**). Changing both PPI and alginate/magaldrate led to a response rate of 62.5%. When patients were treated with alginate or magaldrate without PPI, changing alginate to magaldrate or vice

versa was associated with a higher response rate (76.9%) than the other changes (**Table 2**).

The baseline RSS was predictive of the 3-month RSS ($r_s = 0.766$; $P = .001$), and the 6-month RSS ($r_s = 0.580$; $P = .001$). There were significant positive associations between the number of proximal acid ($r_s = 0.314$; $P = .014$) and nonacid ($r_s = 0.351$; $P = .006$) reflux events and the baseline RSS. Similarly, the number of proximal acid events was associated with the 3-month RSS ($r_s = 0.352$; $P = .005$).

Discussion

In clinical practice, approximately 40% of patients who underwent a well-conducted 3-month LPRD treatment do not experience symptom relief.⁵ However, it has been shown that the symptoms commonly improve after 4 to 8 weeks of treatment in responder patients.^{2,20} The management of patients with refractory LPRD remains challenging, as most otolaryngologists double PPI dose, or change PPI molecule or PPI brand without achieving meaningful improvement in response rates.^{5,21-23}

Based on a database of 334 LPRD patients prospectively followed throughout a 3- to 9-month therapeutic

Table 1. Patient Features

Characteristics	Patients (N = 74)
Mean age (range, years)	52.6 ± 15.5
Body mass index (mean, SD)	24.3 ± 4.2
Gender (N, %)	
Male	38 (51.4)
Female	36 (48.6)
Severity of reflux (RSS-QoL)	
Mild reflux (6-25)	17 (23.0)
Moderate reflux (26-38)	32 (43.2)
Severe reflux (>38)	25 (33.8)
Gastrointestinal endoscopy	N = 55 (%)
Normal	16 (29.1)
Esophagitis	26 (47.3)
Hiatal hernia	20 (36.4)
LES insufficiency	28 (50.9)
Gastritis	18 (32.7)
<i>Helicobacter pylori</i> infection	2 (3.6)
HEMII-pH features (mean, SD)	
Pharyngeal events	
Pharyngeal acid reflux events	14.2 ± 16.7
Pharyngeal nonacid reflux events	7.8 ± 10.8
Total number of pharyngeal events	33.3 ± 29.8
Position events	
Pharyngeal event upright	32.5 ± 29.0
Pharyngeal event supine	4.3 ± 5.5
GERD	
Number of patients (%)	33 (44.6)
Percentage of time with distal pH < 4	10.0 ± 14.1

Abbreviations: GERD, gastroesophageal reflux disease; N, number; RSS-QoL, Reflux symptom score-Quality of Life; SD, standard deviation.

Table 2. Treatment Regimens

Baseline unsuccessful treatment	N (%)	Second therapeutic regimen	N (%)	Second line therapeutic response				
				No response	Mild	Moderate	High	Tot response
PPI A & Alginate/Magaldrate	52 (67.5)	PPI A & Magaldrate/alginate (change)	28	9 (32.1)	6 (21.4)	4 (14.3)	9 (32.1)	19 (67.9)
		PPI B (change) & Alginate/magaldrate	8	5 (62.5)	2 (25.0)	0 (0)	1 (12.5)	3 (37.5)
		PPI B (change) & Magaldrate/alginate (change)	8	3 (37.5)	1 (12.5)	2 (25.0)	2 (25.0)	5 (62.5)
		Magaldrate/Alginate (change)	8	3 (37.5)	1 (12.5)	1 (12.5)	3 (37.5)	5 (62.5)
Alginate/Magaldrate	20 (26.0)	Magaldrate/Alginate (change)	13	3 (23.1)	3 (23.1)	2 (15.4)	5 (38.5)	10 (76.9)
		PPI A (add) & Magaldrate/alginate (change)	3	1 (33.3)	0 (0)	1 (33.3)	1 (33.3)	2 (66.6)
		PPI A (add) & Alginate/magaldrate	4	2 (50)	2 (50)	0 (0)	0 (0)	2 (50)
PPI A	5 (6.5)	PPI A & Magaldrate/alginate (add)	2	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)
		Alginate/Magaldrate	3	2 (66.6)	1 (33.3)	0 (0)	0 (0)	1 (33.3)

The few patients unsuccessfully treated with PPI without alginate or magaldrate reported response rate of 33.3% when treated with alginate or magaldrate from 3- to 6-month posttreatment. The PPI A and B doses were similar (40 mg in the morning). In the PPI A & Alginate/magaldrate group, patients initially treated with alginates changed into magaldrate in the second therapeutic regimen and vice versa. Abbreviations: N, number; PPI, proton pump inhibitor(s).

Table 3. Reflux Symptom Score Changes

Symptom scores	Baseline	3 mo	P value	6 mo	P value
Otolaryngological Reflux Symptom Score	57.2 ± 37.4	62.4 ± 37.0	NS	50.4 ± 42.7	.001
Digestive Reflux Symptom Score	35.6 ± 31.9	40.3 ± 35.3	NS	29.3 ± 30.8	.001
Respiratory Reflux Symptom Score	17.0 ± 18.6	22.3 ± 22.4	NS	12.9 ± 18.2	.001
Reflux Symptom Score-QoL	36.3 ± 18.5	33.4 ± 16.6	NS	26.7 ± 21.7	.001
Reflux Symptom Score	110.3 ± 61.2	123.9 ± 69.9	NS	90.4 ± 76.0	.001

The scores are the mean and standard deviation of all recalcitrant patients. The change of drugs occurred at 3 months. Abbreviations: mo, month; NS, nonsignificant; QoL, quality-of-life.

Table 4. Reflux Sign Assessment Changes

Reflux signs	Baseline	3 mo	P value	6 mo	P value
Oral cavity subscore	5.8 ± 2.0	4.8 ± 2.5	NS	4.6 ± 2.0	NS
Pharyngeal cavity subscore	9.3 ± 4.3	7.6 ± 3.6	NS	7.5 ± 4.1	NS
Laryngeal subscore	13.1 ± 5.6	9.8 ± 5.4	.001	7.2 ± 5.0	.001
RSA total score	27.4 ± 8.2	22.0 ± 8.0	.001	19.0 ± 8.1	.017

The scores are the mean and standard deviation of all recalcitrant patients. The change of drugs occurred at 3 months. Abbreviations: NS, nonsignificant; RSA, reflux sign assessment.

period, the present study supported that changing the drug class was associated with a 61% response rate in patients with refractory LPRD after 3 months of treatment. The response rates vary according to the class changes, and the highest effectiveness was observed when alginates were changed into magaldrate or vice versa. The efficacy of alginate and magaldrate can be related to the LPRD profiles of most patients who have weakly acidic

or alkaline pharyngeal reflux events at the 24-hour HEMII-pH. The existence of several LPRD patterns led to recent studies using personalized treatments for LPRD according to the 24-hour HEMII-pH findings, which was associated with high therapeutic success rates.¹⁴ Moreover, a recent study reported that patients with LPRD have variable concentrations of gastroduodenal enzymes in the upper aerodigestive tract fluids (eg, bile

salts, pepsin, or elastase),²⁴ which is particularly relevant when considering the weakly acidic to alkaline patterns of pharyngeal reflux events. From a pharmacological standpoint, the results found in using alginates or magaldrates may be explained by the significant physiological differences between magaldrate and alginate. Magaldrate has antacid, bile-sequestering, antipeptic, mucosa growth-stimulating factors, and cytoprotective activities by neutralizing chlorohydric acid in the stomach and reducing gastric pH.^{21,25} The sequestration of bile acids and pepsin is the primary mechanism of magaldrate in LPRD because pepsin and bile salt induced mucosal inflammation is associated with LPRD.² Alginate properties are based on its interaction with gastric acid to form a strong viscous gel (alginate raft), which floats on the top of the stomach contents and effectively reduces through a physical mechanism the reflux of the gastric contents into the esophagus and pharynx.²⁵ When compared to magaldrate, alginate does not have bile or pepsin sequestering activity through a physical mechanism.²⁵ In that way, magaldrate may have higher efficacy in patients with high bile acid concentration in laryngopharyngeal fluids, reducing the bile acid-induced inflammation and related symptoms. The interest in using several types of drugs was supported by Giannini et al who observed a variable response to alginate versus magaldrate in GERD patients with total disappearance of symptoms in 81.6% and 73.9% of cases treated with sodium alginate and magaldrate, respectively.²⁵ The authors notably observed that sodium alginate acted more quickly than magaldrate in relieving GERD symptoms and showed a tendency toward a more prolonged duration of action and a higher level of efficacy in patients with acid GERD.²⁵ However, they also reported that alginate and magaldrate were comparable in terms of symptom severity reduction despite different physiological mechanisms.²⁵

Other authors investigated the effectiveness of changing the PPI molecule in refractory GERD.²¹ The potential effectiveness of changing the PPI molecule was based on patient variability in their clinical response to different molecules.²⁶ However, a recent meta-analysis did not demonstrate significant differences in the effectiveness of acid suppression when comparing equivalent doses of different types of PPIs, which indicated that they can be used interchangeably in refractory GERD.²⁶ In this study, changing PPI molecule was associated with the lowest therapeutic response, which corroborated the findings of the GERD literature.²⁶ Physiologically, PPIs inhibit the proton pump and reduce the pH of refluxed material, but they do not change the number and duration of reflux events and their related enzymatic content.²⁶ In LPRD, most pharyngeal events are weakly acidic or alkaline^{6,7,14} and the saliva of LPRD patients is more alkaline than that of healthy individuals.^{25,27} In that way, changing PPI molecules does not make sense in reflux disease that is already weakly acidic or alkaline. Comparing our results with those of the current literature is still limited for

several reasons. On the one hand, there is no study investigating the effectiveness of alginate-to-magaldrate changes in symptom relief of refractory GERD or LPRD. On the other hand, the comparisons with the GERD literature remains limited according to the differences between LPRD and GERD in terms of pathophysiology, and clinical response.

The findings of the present study can be important for clinical practice and from an economical standpoint. Suggesting that changing the drug class could be an alternative therapeutic approach to increasing the drug dose or continuing the same treatment can lead to more cost-effective approaches in LPRD management. Indeed, an increase in drug dose may be associated with a higher proportion of adverse events, especially in PPI therapy,²⁸ while antacids and alginate are known to have less serious adverse events than PPIs.²¹ Further studies investigating the effectiveness, safety, and the cost of these therapeutic strategies are needed.

In the same way, the use of 24-hour HEMII-pH for documenting the features of LPRD (acid, weakly acidic, or alkaline) and indicating the most appropriate primary therapeutic regimen could be more cost-effective than previously thought. The medical record review performed in the present study revealed that 74/334 patients had refractory LPRD after a 3-month primary personalized treatment with a therapeutic success rate of 77.8%. This rate is higher than those reported in the literature^{4,5} because the primary therapeutic regimen was based on the HEMII-pH findings, considering the presence of GERD, and the type of LPRD (acid, weakly acidic, or alkaline). The use of personalized treatment in patients who underwent 24-hour HEMII-pH is in line with the development of personalized medicine,²⁹ which has previously been associated with a high therapeutic response rate.^{14,30} The consideration of personalized medicine in LPRD is indirectly supported by recent publications that suggested that LPRD has variable clinical patterns regarding the reflux features (enzymes, pH),^{6,7,31} gender,³² age,³² or weight.³³

To the best of our knowledge, there is no similar study investigating the effectiveness of drug class changes in the LPRD literature, which can be considered as a strength. The use of validated patient-reported outcome questionnaires and clinical instruments is an additional strength. Note that our analysis reports that RSA total score improved before symptoms, which supports the lack of association between symptoms and signs,³⁴ and a potential minimal efficacy of the primary treatment.

The lack of a control group that includes refractory LPRD patients with continuing treatment or increasing medication doses is the primary limitation of the study. Theoretically, increasing doses or continuing the same treatment from 3 to 6 additional months could lead to additional symptom improvements. However, this finding is currently controversial based on studies reporting poor responses to increased medication doses,^{5,21,23} while the

effectiveness of a LPRD therapy is commonly observed after 4 to 8 weeks of treatment.^{2,20} The present study only included patients who fully adhered to the treatment (diet and medication). In practice, we had no possibility to control for patient adherence, which can be considered as an additional limitation. Another important point concerns the limited availability of antacids, such as magaldrate, in some countries. Importantly, if magaldrate is not available, other antacids can be used, such as algedrate which neutralizes acid, increasing the stomach pH, and inactivating lysolecithin and bile salts. However, to date, there is no study comparing magaldrate and algedrate. Lastly, the formulation of the medication was not considered in the evaluation of the therapeutic effectiveness rate. Gaviscon is available in liquid or tablet form, and the impact of the formulation on the therapeutic responses cannot be formally excluded. This is an additional topic for further investigations that needs to be kept in mind, considering that alginates available on the US and European markets are different, with European ones containing higher alginate concentrations and potentially leading possibly to a higher efficacy.³⁵

Conclusion

The findings of this study may reasonably support the notion that changing drug classes, especially alginate-to-magaldrate, is an effective therapeutic approach for patients with refractory LPRD after a 3-month well-conducted primary treatment. Future controlled studies are needed to compare the safety, effectiveness, and cost implications of changing drug class, continuing treatment, and increasing drug doses.

Author Contributions

Emilie Herman, design, acquisition of data, data analysis & 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; **Sven Saussez**, design, acquisition of data, data analysis & 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; **Jérôme R. Lechien**, design, acquisition of data, data analysis & 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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