# EMERGING FROM GASTROESOPHAGEAL REFLUX (EMERGE): AN ITALIAN SURVEY - II THE VIEWPOINT OF THE PATIENT

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**Gastroesophageal reflux disease (GERD) is a very common disease, as about a quarter of the Western population has GERD symptoms at least weekly and GERD is the most frequent reason for outpatient gastroenterology consultation. GERD treatment is based on proton pump inhibitor (PPI) use, but PPI may be ineffective in some patients and potentially unsafe if administered for very long time. A new medical compound (Marial®) has been introduced on the Italian market. This product contains magnesium alginate and a phytopolymer: it may be able to repair ulcer/erosion, protect mucosal tissue, and contrast acid contents. The current survey was conducted on a large group of GERD patients visited at 56 Italian gastroenterological offices. Patients were treated with PPI alone, PPI plus add-on, or Marial® for 4 weeks: the choice was decided by each gastroenterologist on the basis of the best practice criterion. A reflux symptoms index (RSI) questionnaire was used to weekly assess the clinical features. Marial® and PPI plus add-on significantly reduced RSI scores, from the second week. Noteworthy, Marial® was more effective than PPI plus add-on. In conclusion, the current survey demonstrated that patients with GERD perceived a significant improvement of GERD symptoms measured by the RSI questionnaire. Marial® was as effective as PPI plus add-on.**

*Key words: gastroesophageal reflux disease, patients, RSI, PPI, Marial®*

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**DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.**

To the Editor,

Gastroesophageal reflux disease (GERD) is very common, indeed about 25% of the Western population has GERD symptoms at least weekly (1). In addition, GERD is the most frequent reason for outpatient gastroenterology consultation (2). From a therapeutic point of view, the current guidelines recommend GERD medical management as first step with proton pump inhibitors (PPIs) that are the most effective therapy for erosive esophagitis (3-5). However, there is convincing proof that in some patients with GERD symptoms, especially those with non-erosive reflux disease (NERD), the acid suppression by PPIs may be not as effective (3). Therefore, an alternative approach for treating symptomatic GERD could be to try to impede the flow of acidic refluxate. In this regard, alginic acid derivatives, or alginates, are able to treat GERD by creating a mechanical barrier that displaces the post-prandial acid pocket (6). Their mechanism of action is based on the fact that in the presence of gastric acid, they precipitate into a gel and form a raft that localizes to the acid pocket in the proximal stomach (7). Although they have been available in many countries over-the-counter for several decades, often in combination with antacids, this class of medications has recently raised renewed research interest (8). In fact, providing an impediment to distal oesophageal acid exposure, alginates may be superior to other measures or particularly useful as an additional option for patients with GERD not responding to anti-secretory therapy (9). In other words, even though the current treatment guidelines recommend prescribing PPI for acid suppression as first line therapy in patients with chronic GERD symptoms, it is well known that many patients may have only intermittent or mild/moderate symptoms and so could need a less aggressive treatment. A recent meta-analysis provided evidence that alginates alone may provide superior benefit over antacids and therefore they could be considered as an initial treatment for patients with mild/moderate GERD symptoms for whom chronic acid suppression should be either undesirable or deemed unnecessary (9). In this context, a new medical compound has been recently launched in Italy: Marial® (manufactured by Aurora, Milan, Italy) containing magnesium alginate and E-Gastryal®. An Italian survey explored the pragmatic approach of a group of gastroenterologists in GERD management. The aim of this survey analysis was to evaluate the GERD patient's point of view during a course of therapy using the RSI score changes as primary outcome.

## MATERIALS AND METHODS

The current survey was conducted in 56 gastroenterological centers, distributed in the whole of Italy, so assuring a wide and complete national coverage. The gastroenterologists endorsed to the Project EMERGE (Emerging from RGE) were asked to recruit all consecutive patients visited because of GERD.

Patients were consecutively recruited during the specialist visit. The inclusion criteria were: to have a diagnosis of GERD, 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, the doctors had the complete liberty of choosing the preferred medications on the basis of the best practice. All subjects gave informed, signed consent to participate in the study. Three therapeutic options were prescribed: PPI as monotherapy, Marial® as monotherapy, and PPI plus add-on. The add-on options included a miscellany of medication options, including alginates, anti-acids, prokinetics, antiH2, and Marial®.

The course of treatment lasted 4 weeks. Medications were taken following the specific indications. Patients were asked to complete weekly the RSI questionnaire, therefore, 5 RSI scores were available. They were collected in the specialist's 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 issue of JBRHA.

Demographic and clinical characteristics were described using means with SDs or SEs for normally-distributed continuous data (i.e. age or percentage of RSI reduction) 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; Mann U Whitney test was used to compare percentage of changes in RSI. 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

A total of 771 patients (50.87% males, 49.13% females, mean age 49.8 years) took the prescribed therapy, concluded the treatment course, and completed the RSI questionnaire.

Fig. 1 shows the distribution of the different therapeutic options prescribed during the gastroenterological visit. Most patients (63%) were treated with PPI plus add-on, about a quarter with Marial® alone, 7.6% with PPI as monotherapy, and only 3.5% with a miscellany.

Considering the entire patient cohort, a time-dependent significant reduction in the RSI score after the treatment is reported in Fig. 2A ($p<0.0001$).

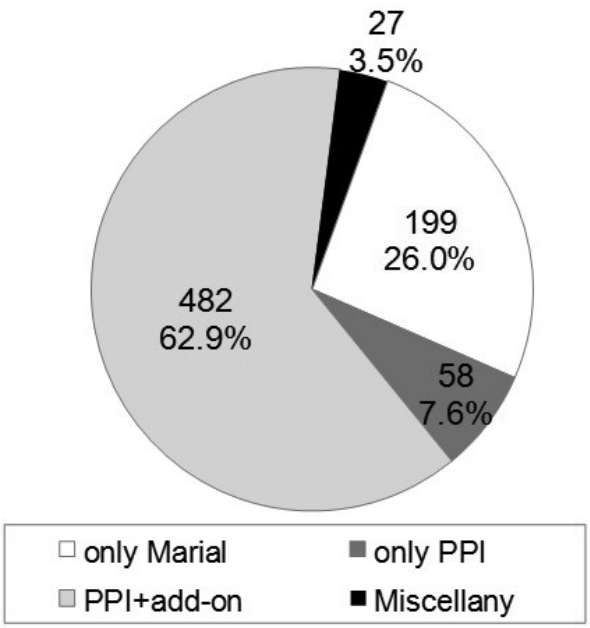


**Fig. 1.** *Distribution of the different treatments prescribed by the gastroenterologists.*

In particular, there was 37.8% reduction of RSI score at the end of the course.

Fig. 2B shows the trend of the total RSI values in patients treated with Marial® as monotherapy and with PPI plus add-on. A time-dependent decrease in RSI total score was observed either after Marial® as monotherapy or with PPI plus add-on. Marial® as monotherapy was able to induce a higher total RSI score reduction as compared to that observed after treatment with PPI plus add-on. This was true starting after 1 week treatment.

Changes in RSI values before and after 4 week-treatment with Marial® as monotherapy was statistically significant for each single symptom (Fig. 3A) ($p<0.001$, each comparison). A similar result was found evaluating PPI plus add-on treatment (Fig. 3B) ($p<0.001$, each comparison).

The percentage of RSI reduction in i) breathing difficulties or choking episodes, ii) difficulty swallowing food, liquids, or pills, iii) clearing throat or iv) hoarseness or a problem with voice was significantly higher in patients treated with Marial® as monotherapy as compared to those treated with PPI plus add-on (Fig. 4).

## DISCUSSION

GERD is one of the most common diseases encountered in both the outpatient and inpatient settings (10, 11). The first-line treatment of gastroesophageal reflux disease continues to be the anti-secretory drugs, most commonly proton pump inhibitors (PPIs). Of course, dietary and lifestyle modifications, including avoidance of acidic foods, carbonated beverages, alcohol, spicy food, and tobacco, in any case continue to be recommended. Weight loss for patients with recent weight gain or BMI >25, avoiding lying down within 2–3 h of meals, and bedhead elevation to improve nocturnal symptoms are also effective interventions that can be recommended (12). Recently, long-term safety of PPIs has been called into question with some evidence of increased infectious complications and nutritional deficiencies, leading some to advocate caution with long-term use of PPIs in elderly,

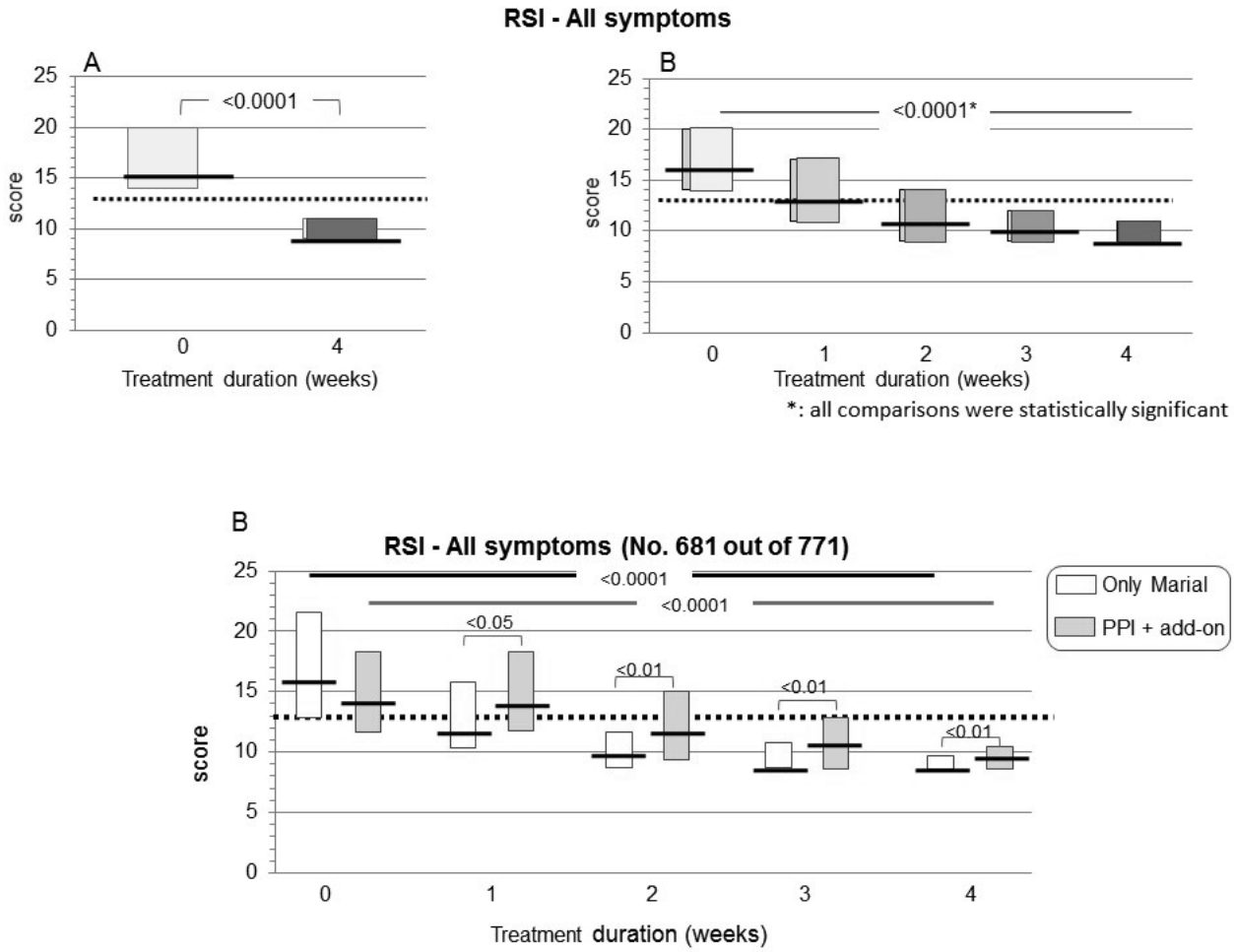


**Fig. 2.** ***A)*** *Total RSI value in all patients at baseline and after 4 weeks (i.e. end of the therapy) (panel A) and total RSI weekly trend over time (panel B).* ***B)*** *Trend of the total RSI values in patients treated with Marial as monotherapy and with PPI plus add-on.*

malnourished, immune-compromised, chronically ill, and osteoporotic patient populations (13, 14).

Very recently, a new medical compound has been presented on the Italian market: Marial®. This novelty has suggested the importance of evaluating its positioning in the therapeutic options for GERD. The current survey was conducted in a real-world setting, such as outpatients visited at 56 Italian gastroenterological clinics.

The primary outcome demonstrated that Marial® was prescribed in about a quarter of the visited patients, whereas PPI plus add-on remained the preferred option as prescribed in about one third of patients. Both Marial® and PPI plus add-on were able to significantly reduce RSI score; interestingly, a significant RSI diminution was remarkable from the first week. Noteworthy, Marial® induced a more significant RSI reduction than PPI plus add-on considering both the total RSI score and some single symptoms. This finding is surprising, even though partially depending on relatively lower RSI values at baseline (but without significant difference). Instead, to support this difference, Marial®-treated patients had lower GIS scores than PPI-plus-add-on-treated patients as evidenced during the visits.

The present survey has some limitations: the open

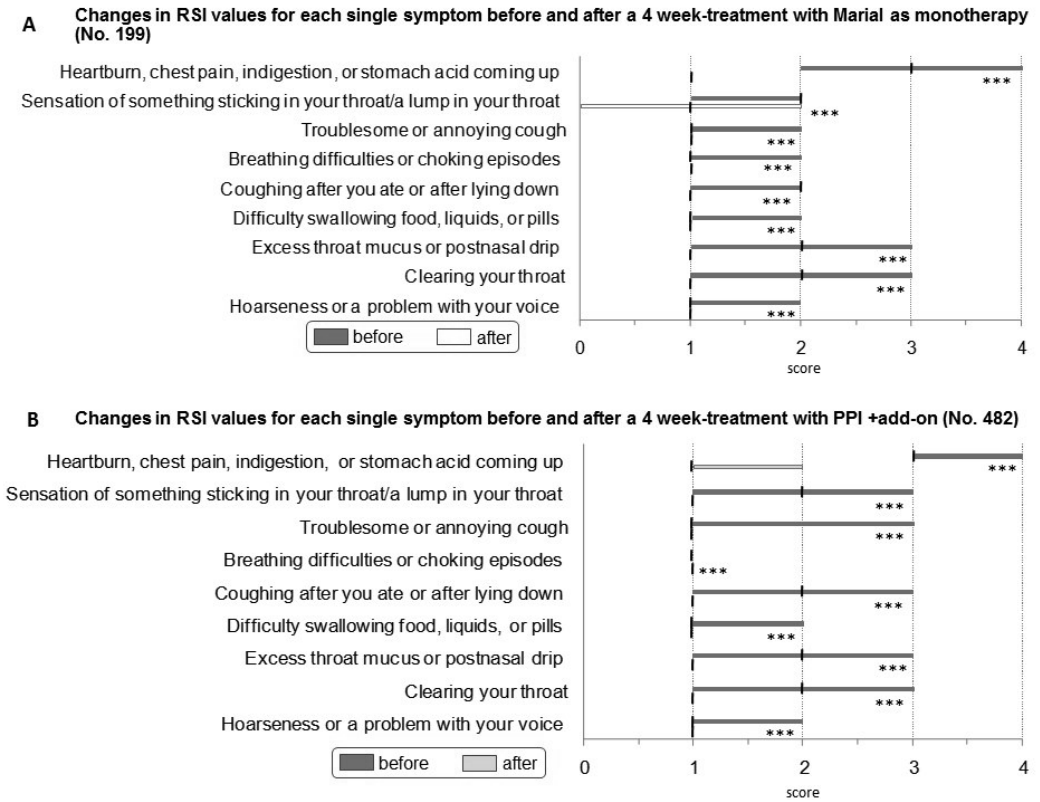


**Fig. 3.** ***A)*** *Changes in RSI scores for each single symptom evaluated before and after the 4-week treatment with Marial®.* ***B)*** *Changes in RSI scores for each single symptom evaluated before and after the 4-week treatment with PPI plus add-on.*

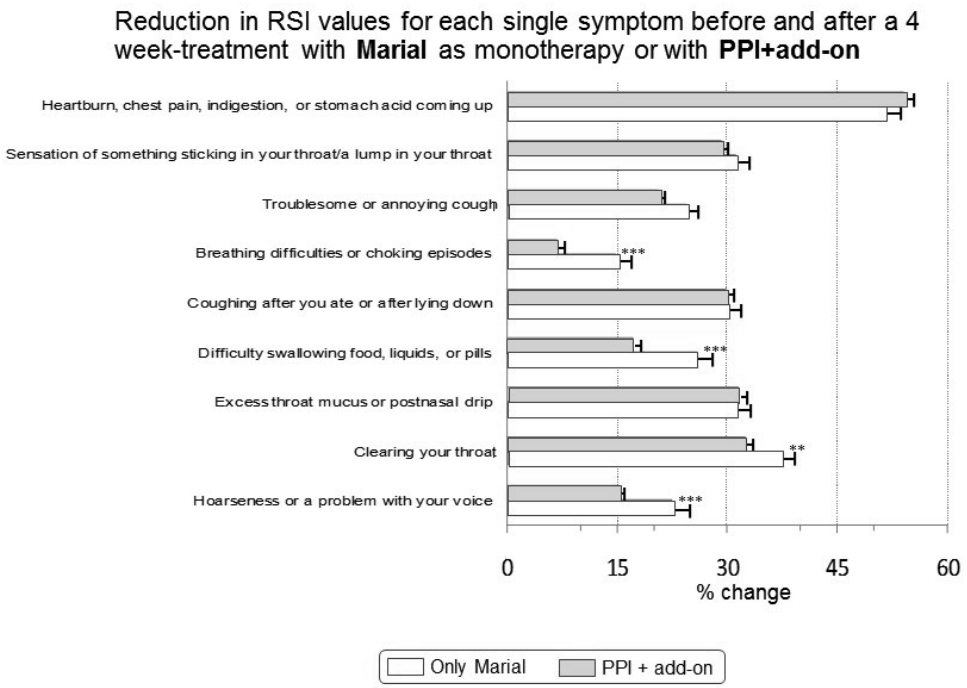


**Fig. 4.** *Percentages of RSI reduction for each single symptom in patients treated with Marial® as monotherapy and with PPI plus add-on.*

design, the lack of randomization and placebo-group, the lack of objective evaluation and biomarkers. Therefore, further studies should be conducted to adequately fill these shortcomings.

In conclusion, the current survey demonstrated that patients with GERD perceived a significant improvement of GERD symptoms as measured by the RSI questionnaire. Marial® was as effective and rapid as PPI plus add-on. So, Marial® could be considered a reasonable option in the management of GERD.

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