• Clinical Research •

A combined treatment for patients with dry eye and associated laryngopharyngeal reflux: a real-life approach

Giorgio Ciprandi[1], Stefano Bonini[2], Irene Schiavetti[3], Valerio Damiani[4], Study Group on Dry-Eye Pragmatical Management

[1]Allergy Clinic, Casa di Cura Villa Montallegro, Genoa 16145, Italy
[2]Ophthalmology Complex Operative Unit, University Campus Bio-Medico, Rome 00100, Italy
[3]Health Science Department, University of Genoa, Genoa 16142, Italy
[4]Medical Department, DMG, Pomezia 00070, Italy
Correspondence to: Giorgio Ciprandi. Via Boselli 5, Genoa, 16146, Italy. gio.cip@libero.it
Received: 2023-06-07 Accepted: 2023-07-25

Abstract

● **AIM:** To evaluate the efficacy and tolerability of administering a combined therapy in patients with dry eye syndrome (DES) and associated laryngopharyngeal reflux (LPR).

● **METHODS:** The study was retrospective, open, observational, and conducted in a real-life setting. Patients had pathological symptom assessment in dry eye (SANDE) and reflux symptom index (RSI) at baseline. Patients were re-assessed after 1mo and at the end of treatment. The treatment consisted of a three-month course based on the combined therapy: Gastroftal eye drops, one drop three times a day, and Gastroftal tablets, two tablets after lunch and two tablets after dinner. Tear break-up-time (TBUT) test, Schirmer test, RSI, and SANDE questionnaire were evaluated.

● **RESULTS:** The study included 253 patients. The mean age was 58±11.19y. TBUT test score and Schirmer's test significantly increased (both P<0.001) after 1mo and at the end of treatment. The RSI score and SANDE scores significantly decreased (both P<0.001) after 1mo and at the end of treatment.

● **CONCLUSION:** The current, retrospective, and open study shows that combined therapy using Gastroftal eye drops and tablets could represent a valuable option in managing patients with DES associated with LPR.

● **KEYWORDS:** dry eye syndrome; laryngopharyngeal reflux; combined therapy; hyaluronic acid; alginate; Camelia sinensis; real-life

DOI:10.18240/ijo.2023.10.09

Citation: Ciprandi G, Bonini S, Schiavetti I, Damiani V, Study Group on Dry-Eye Pragmatical Management. A combined treatment for patients with dry eye and associated laryngopharyngeal reflux: a real-life approach. *Int J Ophthalmol* 2023;16(10):1616-1622

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a widespread condition in the general population[1]. GERD encompasses a spectrum of conditions with different localizations: limited to the esophagus (the typical GERD), or extra-esophageal ones, with various symptoms, including sore throat, chronic cough, asthma, and pharyngeal globus[2]. Laryngopharyngeal reflux (LPR) is an expression of extraesophageal GERD[3]. LPR constitutes a relevant medical condition as approximately 10% of patients with ear, nose, and throat disorders and 50% of patients with voice problems suffer from LPR[4-5].

There are different theories about the pathophysiological mechanisms. The reflux theory envisaged that the refluxate induces direct injury to the larynx through the micro-aspiration of acid, bile acids, and pepsin[6]. The reflex theory proposed that acidification of the distal esophagus may induce symptoms in the larynx through a vagal reflex[7].

Interestingly, it has been shown that LPR can lead to nasolacrimal duct obstruction[8]. Consistently, patients with acquired primary nasolacrimal duct obstruction may have a higher prevalence of GERD than the general population[9]. Finally, a study demonstrated a positive association between ocular symptom severity and reflux symptom index (RSI) scores[10].

Pepsin is a proteolytic enzyme produced in the stomach alone. Therefore, detecting pepsin in extra-gastric areas is considered a reliable diagnostic biomarker of gastric reflux and a pathogenic mediator of reflux-related damage[11]. Accordingly, pepsin has so far been identified in the larynx, pharynx, sinuses, saliva, and inner ear of subjects with LPR[12]. Thus, it was hypothesized that pepsin could also be present in the eye and play a role in ocular disorders detected in association

with LPR. As proof of this concept, pepsin has also been detected in the tears of adults and children with LPR[13-14]. It may be imagined that pepsin could arrive at the ocular level by passing through the nasal cavity, the inferior meatus, and the nasolacrimal duct. Supporting this theory, *helicobacter pylori* has also been detected in the ocular secretions of dyspeptic patients[15]. Consequently, managing patients with LPR and associated ocular disorders represents an urgent challenge for physicians and patients[16]. In this regard, dry eye syndrome (DES) is a common medical condition sometimes associated with LPR[17]. DES is usually characterized by visual disturbances, ocular irritation, ocular pain, photophobia, and excessive tearing, and it significantly affects the quality of life[18]. DES recognizes different causes and pathophysiologic mechanisms. An ocular surface inflammation is a common feature. In this regard, reflux of gastric material (acid and proteolytic) could play an important pathogenetic role.

A preliminary experience demonstrated that combining the treatment of DES and LPR could be a valuable option[19]. As a result, managing LPR, if associated, could improve also DES. Therefore, the present real-life study retrospectively evaluated the efficacy and tolerability of administering a combined therapy consisting of topical application of Gastroftal eye drops containing hyaluronic acid, magnesium alginate, and *Camellia sinensis* extract and oral administration of Gastroftal tablets containing magnesium alginate and simethicone in patients with DES and associated LPR.

SUBJECTS AND METHODS

Ethical Approval The present study was conducted as retrospective and observational. The study was conducted following the principles outlined in the Declaration of Helsinki (2008). Patients gave their signed consent for the privacy, according to the national rules.

Patients The study included patients with DES associated with LPR and evaluated in ophthalmological primary care settings. Twelve ophthalmologists retrospectively included consecutive patients who visited them in their daily practice.

Inclusion criteria were adult age (18-80y) and pathological SANDE and RSI score. Exclusion criteria were comorbidities, including glaucoma, ocular infections, allergic conjunctivitis, malignancy, ophthalmological and/or nasal surgery, diabetes mellitus, autoimmune diseases, pregnancy, breastfeeding, contact lenses use, and concomitant treatments, including decongestants, topical corticosteroids, non-steroidal anti-inflammatory drugs (NSAID), antihistamines, beta-blockers, diuretics, antidepressants, hormone replacement therapy, and immunosuppressive agents.

Design The baseline visit included history, mainly concerning ophthalmological diseases, risk factors, and current treatments; ophthalmological examination, including Schirmer's test and standard tear break-up-time (TBUT) test; and administration of SANDE and RSI questionnaires.

The patients underwent a 3mo treatment based on the combined therapy: Gastroftal eye drops, one drop three times a day, and Gastroftal tablets, two tablets after lunch and two tablets after dinner.

The study assessment was carried out at baseline (V0), after 1mo of treatment (V1), and after 3mo of treatment (V2). At these times, patients answered the questions contained in the Symptom Assessment in Dry Eye (SANDE) questionnaire and the RSI questionnaire. The investigators also checked and assessed treatment compliance and any withdrawal of patients from the study. Any adverse events were recorded throughout the study.

Symptom perception was evaluated using the SANDE questionnaire utilizing a 100 mm horizontal visual analogue scale (VAS) technique (0=absence, 100=maximum) to quantify the severity and frequency of ocular dryness and/or irritation[20].

RSI is a self-administered nine-item questionnaire developed by Belafsky for assessing symptoms in patients with reflux disease[21]. It is so simple that it can be completed in less than 1min. Each item's scale ranges from 0 (no problem) to 5 (severe problems), with a maximum score of 45. It has been concluded that RSI has high reproducibility and validity for the diagnosis of reflux if an RSI score >13 is defined as abnormal[22]. Therefore, RSI may be a practical tool for patients with suspected LPR[23].

Schirmer test was performed without topical anesthesia by placing a narrow filter paper strip (5×35 mm^2 strip of Whatman #41 filter paper) in the inferior cul-de-sac. Normal values should be >5 mm/5min[24].

The standard TBUT measurement was performed by instilling a fluorescein drop into the inferior fornix[25]. The time-lapse between the last blink and the appearance of the first randomly distributed dark discontinuity in the fluorescein-stained tear film was measured three times, and the mean value of the measurements was calculated. Normal values should be >10s.

The patients measured their perception of symptom improvement, treatment tolerability, and treatment liking at V1 and V2. Patients used a VAS to assess their perceptions. The 0 score meant the best response, 10 the worst response.

Statistical Analysis Continuous variables were summarized as mean with standard deviation and median with range. Categorical data were expressed with frequency and percentage. A generalized linear mixed model is applied to evaluate the time effect on different assessments measured at V0, V1, and V2. The model includes time as a fixed effect, age as a fixed covariate, and subject and eye (right or left) as random effects. In addition, specific risk factors that resulted significant in

Table 1 Demographic and clinical data at the screening visit

Parameters	Mean±SD
Age, y	58.0±11.19
SANDE frequency of symptoms	57.8±17.28
SANDE symptom intensity	49.1±18.88
RSI score	18.04±4.41
Pathological RSI, *n* (%)	253 (100.0)
TBUT score (right eye)	7.0±2.37
TBUT (right label), *n* (%)	
Normal value	45 (19.6)
Abnormal value	185 (80.4)
TBUT score (left eye)	7.0±2.45
TBUT score (left label), *n* (%)	
Normal value	43 (18.6)
Abnormal value	188 (81.4)
Schirmer's test score (right eye)	7.8±2.58
Schirmer's test score (right label), *n* (%)	
Normal value	58 (25.6)
Abnormal value	169 (74.4)
Schirmer's test score (left eye)	7.9±2.71
Schirmer's test score (left label), *n* (%)	
Normal value	59 (25.9)
Abnormal value	169 (74.1)

SANDE: Symptom assessment in dry eye; RSI: Reflux symptom index; TBUT: Tear break-up-time.

Table 2 Risk factors

Risk factors	*n* (%)
Use of computer	186 (73.5)
Computer, frequency of use	
Low (1-2h)	11 (5.9)
Medium (3-5h)	41 (22.0)
High (6h or more)	113 (60.8)
Not specified	21 (11.3)
Use of artificial lighting	171 (67.6)
Artificial lighting, frequency of use	
Low (1-2h)	3 (1.8)
Medium (3-5h)	29 (17.0)
High (6h or more)	110 (64.3)
Not specified	29 (17.0)
Alcohol consumption	95 (37.5)
Alcohol, quantity/die	
Less than half-litre	65 (68.4)
Half-litre or more	21 (22.1)
Not specified	9 (9.5)
Years of alcohol consumption (range)	25.0 (3.0-40.0)
Smoking habits	123 (48.6)
Cigarettes per day (range)	13.6±6.44, 12.0 (3.0-40.0)
Years of smoking (range)	20.0 (5.0-50.0)
GERD diagnosis	80 (31.6)
GERD duration, y (range)	3.0 (0.0-23.0)
GERD therapy	63 (24.9)
Positivity for *Helicobacter pylori*	51 (20.2)
Helicobacter pylori duration of infection, y (range)	5.5 (0.0-29.0)
Therapy for *Helicobacter pylori*	32 (12.6)
LPR duration, y (range)	5.5 (0.0-29.0)

GERD: Gastroesophageal reflux disease; LPR: Laryngopharyngeal reflux.

univariate analysis were implemented as a fixed effect in the analysis (GERD diagnosis for Schirmer's test, smoking habits for RSI score, and smoking habits and use of artificial lighting for frequency and severity of SANDE questionnaire).

Multiple comparisons are adjusted using sequential Bonferroni. Two-sided *P*-values of less than 0.05 are considered statistically significant. The IBM SPSS Statistics V.24.0 (IBM Corp. Released 2016, Armonk, New York, USA: IBM Corp) was used for statistical analysis.

RESULTS

The study included 253 patients. The mean age was 58±11.19y. Table 1 reports demographic and clinical data. All recruited patients had pathological scores for both SANDE and RSI questionnaires. The mean scores are in detail reported in Table 1. In addition, the mean TBUT and Schirmer's test values are reported individually for both eyes as an absolute value and a percentage of patients with the pathological result. About 80% of patients had pathological values of the TBUT test and 74% of the Schirmer test.

Table 2 shows the list of risk factors and their frequency. Computer use was widespread, as 73.5% of patients did it. Similarly, the use of artificial lighting was frequent (67.6%). Alcohol consumption, mostly moderate, and smoking were relatively common, 37.5% and 48.6%, respectively. Eighty patients (31.6%) had GERD diagnosis, 20.2% had positivity for *Helicobacter pylori*, and the mean LPR duration was 5.5y.

Table 3 reports the investigated parameters at V1. In addition, treatment adherence was good in 69.5% of patients and discrete in 30.5%. About half of the patients had pathological RSI scores, about 45% had pathological TBUT test, and about 60% had pathological Schirmer's test. The perception of efficacy, tolerability, and liking was good.

Table 4 reports the investigated parameters at V2. In addition, treatment adherence was good in 71% of patients, discrete in 27.1%, and poor in 1.4%. About 37% of patients had pathological RSI scores, about 50% had pathological TBUT test, and about 40% had pathological Schirmer's test. The perception of efficacy, tolerability, and liking was good.

Table 5 reports the comparative analysis of the investigated parameters at different times. In addition, the linear mixed model evaluated the variables associated with changes in every parameter.

The overtime changes of the investigated parameters are

Table 3 Assessments at V1 *n*=177

Parameters	Mean±SD
Treatment executed, *n* (%)	177 (100.0)
Compliance, *n* (%)	
Poor	0
Discrete	54 (30.5)
Good	123 (69.5)
RSI score	13.8±5.20
Pathological RSI, *n* (%)	91 (51.4)
SANDE questionnaire: frequency of symptom score	39.8±18.97
SANDE questionnaire: severity of symptom score	35.3±16.77
TBUT score (right eye)	9.1±2.61
TBUT score (right label), *n* (%)	
Normal value	76 (54.3)
Abnormal value	64 (45.7)
TBUT score (left eye)	9.1±2.66
TBUT score (left label), *n* (%)	
Normal value	75 (54.3)
Abnormal value	63 (45.7)
Schirmer's test score (right eye)	10.0±2.71
Schirmer's test score (right label), *n* (%)	
Normal value	85 (58.2)
Abnormal value	61 (41.8)
Schirmer's test score (left eye)	10.1±2.93
Schirmer's test score (left label), *n* (%)	
Normal value	92 (63.0)
Abnormal value	54 (37.0)
VAS – Improved clinical effectiveness	3.9±3.29, 3.5 (0.0-21.5)
VAS – Tolerability of treatment	2.8±3.05
VAS – Compliance	2.4±2.74
Adverse events	0

SANDE: Symptom assessment in dry eye; RSI: Reflux symptom index; TBUT: Tear break-up-time; VAS: Visual analog score.

Table 4 Assessments at V2 *n*=218

Parameters	Mean±SD
Treatment executed, *n* (%)	214 (98.2)
Compliance, *n* (%)	
Poor	3 (1.4)
Discrete	58 (27.1)
Good	152 (71.0)
Not specified, *n* (%)	1 (0.5)
RSI score (*n*=217)	11.3±4.84
Pathological RSI, *n* (%)	80 (36.9)
SANDE questionnaire: frequency of symptom score	38.3±17.31
SANDE questionnaire: severity of symptom score	27.9±14.81
TBUT score (right eye)	9.5±2.53
TBUT score (right label), *n* (%)	
Normal value	95 (48.5)
Abnormal value	101 (51.5)
TBUT score (left eye)	9.5±2.67
TBUT score (left label), *n* (%)	
Normal value	94 (48.0)
Abnormal value	102 (52.0)
Schirmer's test score (right eye)	10.5±2.88
Schirmer's test score (right label), *n* (%)	
Normal value	122 (61.9)
Abnormal value	75 (38.1)
Schirmer's test score (left eye)	10.4±2.93
Schirmer's test score (left label), *n* (%)	
Normal value	114 (57.9)
Abnormal value	83 (42.1)
VAS – improved clinical effectiveness	3.6±2.84
VAS – tolerability of treatment	3.0±2.62
VAS – compliance	2.5±2.49
Adverse events	0

SANDE: Symptom assessment in dry eye; RSI: Reflux symptom index; TBUT: Tear break-up-time; VAS: Visual analog score.

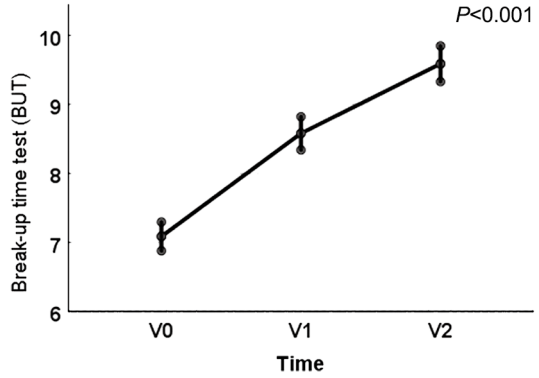

Figure 1 Break-up-time test scores at V0, V1, and V2.

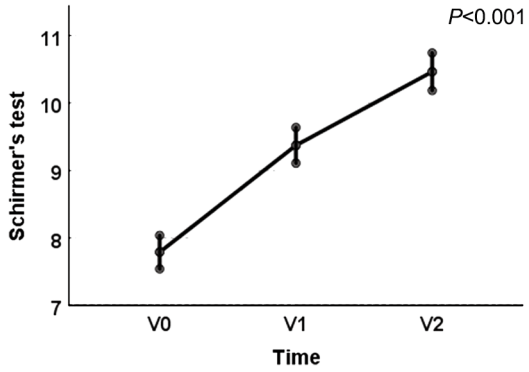

Figure 2 Schirmer's test scores at V0, V1, and V2.

summarized and depicted in Figures 1-4. The TBUT scores significantly and progressively increased over time (Figure 1). Consistently Schirmer's test scores significantly and gradually increased over time (Figure 2). Contrarily, the RSI scores significantly and progressively decreased (Figure 3). Similarly, the SANDE frequency and severity scores significantly and progressively reduced (Figure 4). The treatment was well tolerated, and there was no adverse event related to both medical devices.

DISCUSSION

DES is a frequent ocular condition affecting many of the population. In addition, DES involves bothersome and usually

Table 5 Evaluation of change over time of different assessments

Parameters	V0	V1	V2	Estimated coefficient, *P*
TBUT	7.09 (0.11)	8.58 (0.12)	9.59 (0.13)	V1 *vs* V0: 1.49 (0.10), <0.001; V2 *vs* V0: 2.50 (0.11), <0.001
Schirmer's test	7.79 (0.13)	9.37 (0.14)	10.46 (0.14)	V1 *vs* V0: 1.58 (0.12), <0.001; V2 *vs* V0: 2.67 (0.13), <0.001
RSI score	17.99 (0.21)	13.87 (0.21)	10.96 (0.24)	V1 *vs* V0: -4.12 (0.21), <0.001; V2 *vs* V0: -7.03 (0.24), <0.001
Sande frequency of symptoms	57.95 (1.16)	40.04 (1.54)	38.56 (1.22)	V1 *vs* V0: -17.09 (1.80), <0.001; V2 *vs* V0: -19.39 (1.59), <0.001
SANDE questionnaire: severity of symptom score	48.62 (1.22)	34.81 (1.38)	27.71 (1.06)	V1 *vs* V0: -13.81 (1.72), <0.001; V2 *vs* V0: -20.91 (1.53), <0.001

SANDE: Symptom assessment in dry eye; RSI: Reflux symptom index; TBUT: Tear break-up-time. Descriptive data are expressed as estimated marginal means with standard errors.

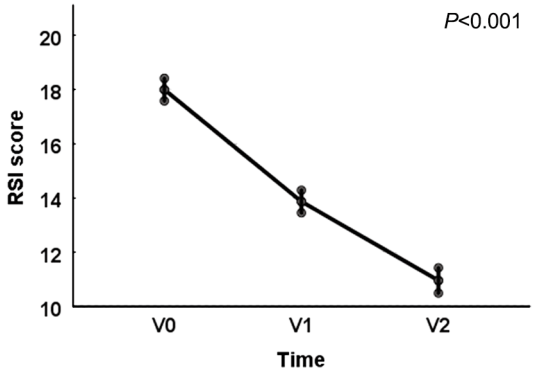

Figure 3 RSI scores at V0, V1, and V2 RSI: Reflux symptom index.

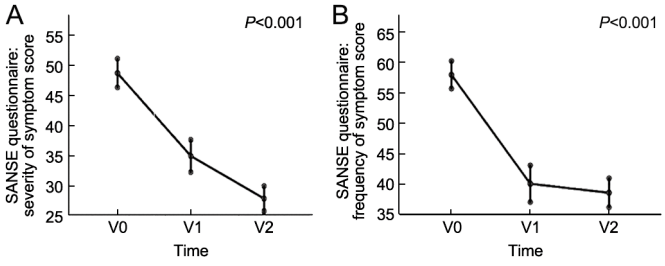

Figure 4 SANDE symptom severity (A) and frequency (B) scores at V0, V1, and V2 SANDE: Symptom assessment in dry eye.

persistent symptoms that negatively impact the quality of life.

The current treatment of DES includes various but only sometimes satisfying therapeutical options. Most treatments are eye drops with lubricant and moisturizing activities. Anti-inflammatories medications are also commonly prescribed. However, most treatments are frequently not resolutive.

DES is a multifactorial disease of the ocular surface characterized by a loss of tear film homeostasis[25]. As a result, the pathogenetic mechanism is complex; a recent systematic review and Meta-analysis identified a series of risk factors for DES[26]. The most prevalent factors included older age, female sex, visual display terminal use, cataract surgery, contact lens wear, pterygium, glaucoma, post-traumatic stress disorders, rosacea, thyroid disease, cancer, and systemic diseases. In addition, autoimmunity and hormone imbalance are relevant pathogenetic factors[27]. Most of these conditions are characterized by an inflammatory reaction. Ocular surface inflammation plays a meaningful role in DES pathogenesis[28]. Accordingly, gastric refluxate in the ocular surface may induce a local inflammatory response. The pepsin presence in the tears of patients with DES and associated LPR suggests a pathogenetic link between these diseases. Acid content and pepsin damage the ocular surface, promoting an inflammatory reaction causing and/or worsening DES.

To support these concepts, there is growing evidence that many patients with DES may have associated LPR. This condition aggravates the clinical picture by also causing further worsening of the severity of ocular symptoms[16]. Eye reflux involves the presence of pepsin in the tear film, which causes inflammation of the conjunctive tissues[14].

The LPR management includes using anti-reflux therapy based on alginates and antiacids[29]. In addition, as LPR patients may have excessive gas production in the stomach, antifoaming agents, such as simethicone, can be helpful. In this regard, the tested oral medical device precisely contains magnesium alginate, potassium bicarbonate, and simethicone. In the gastric acid environment, alginate precipitates as a gel, constituting a raft preventing the reflux of gastric contents[30]. Bicarbonate acts as a buffer reducing gastric acidity[31]. Simethicone significantly contributes to relieving reflux complaints[32].

DES management consists of the possible avoidance of causal factors and the use of medications to dampen inflammation, restore the physiological lacrimal film, and alleviate symptoms[33]. The tested eye drops (Gastroftal) contain hyaluronic acid, magnesium alginate, and *Camelia sinensis* extract. Hyaluronic acid is a relevant constituent of the connective tissue. In addition, hyaluronic acid exerts anti-inflammatory activity, promotes the proliferation of the epithelium, and contributes to remodeling the extracellular matrix[34]. Topically applied magnesium alginate may remove (scavenger effect) pepsin, inhibiting its damage[35-36]. *Camelia sinensis*, a primary component of green tea, provides important anti-oxidant and anti-inflammatory effects[37].

Consequently, combining these medical devices could be an attractive option in managing patients with DES associated with LPR, as this dual strategy may benefit both target organs simultaneously. The present study demonstrated that this combined treatment significantly improved the severity and frequency of both ocular and reflux symptoms and the scores

of ophthalmological tests. Moreover, the current findings consistently confirmed the previous pilot study[19].

These outcomes underscore the clinical relevance of managing patients with both disorders holistically in such a way as to manage and treat the patient organically and as a whole and not in a sectoral manner[38-39].

Again, the present study had some limitations, including the open design, the need for pepsin assessment at the ocular level, the absence of digestive tract evaluation, and the need for a longer follow-up. Moreover, the present study explored the ocular and reflux complaints simultaneously and included an objective investigation of the anterior segment of the eye. In addition, the present study provided a novel therapeutical strategy for managing DES patients with associated LPR. Different studies explored treatments for DES patients but addressed only the eye environment[40-42]. This study was original as it proposed a new approach based on thorough research of possible comorbidity with reflux disease and consequently treating both together.

In conclusion, the current study showed that combined therapy using Gastroftal eye drops and tablets could represent a valuable option in managing patients with DES associated with LPR.

ACKNOWLEDGEMENTS

Study Group on Dry-Eye Pragmatical Management: Ugo Bibbiani, Mirca Reggio Bonacini, Francesco Casanova, Stefano Ciavatti, Marco Del Boccio, Giulio Cesare De Nicola, Luca Di Antonio, Antonella Di Bartolo, Annalisa Fassari, Salvatore Giugno, Maurizio Lo Piano, Domenico Spampinato.

Conflicts of Interest: Ciprandi G, None; **Bonini S,** None; **Schiavetti I**, None; **Damiani V**, employee of DMG; **Study Group on Dry-Eye Pragmatical Management,** None.

REFERENCES

1 Young A, Kumar MA, Thota PN. GERD: a practical approach. *Clevel Clin J Med* 2020;87(4):223-230.

2 Patel DA, Harb AH, Vaezi MF. Oropharyngeal reflux monitoring and atypical gastroesophageal reflux disease. *Curr Gastroenterol Rep* 2016;18(3):12.

3 Lechien Jerome R. Treating and managing laryngopharyngeal reflux disease in the over 65s: evidence to date. *Clin Interv Aging* 2022;17:1625-1633.

4 Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope* 1991;101(4 Pt 2 Suppl 53):1-78.

5 Chen JT, Brady P. Gastroesophageal reflux disease: pathophysiology, diagnosis, and treatment. *Gastroenterol Nurs* 2019;42(1):20-28.

6 Barrett CM, Patel D, Vaezi MF. Laryngopharyngeal reflux and atypical gastroesophageal reflux disease. *Gastrointest Endosc Clin N Am* 2020;30(2):361-376.

7 Wang AM, Wang G, Huang N, *et al*. Association between laryngopharyngeal reflux disease and autonomic nerve dysfunction. *Eur Arch Oto Rhino Laryngol* 2019;276(8):2283-2287.

8 Owji N, Abtahi SMB. Does gastroesophageal reflux contribute to development of acquired nasolacrimal duct obstruction? *Med Hypotheses* 2010;74(3):455-456.

9 Mehta S, Ying GS, Hussain A, Harvey JT. Is gastroesophageal reflux disease associated with primary acquired nasolacrimal duct obstruction? *Orbit* 2018;37(2):135-139.

10 Mazzacane D, Damiani V, Silvestri M, Ciprandi G, Marino P. Eye reflux: an ocular extraesophageal manifestation of gastric reflux. *Int J Ophthalmol* 2018;11(9):1503-1507.

11 Klimara MJ, Randall DR, Allen J, Figueredo E, Johnston N. Proximal reflux: biochemical mediators, markers, therapeutic targets, and clinical correlations. *Ann NY Acad Sci* 2020;1481(1):127-138.

12 Weitzendorfer M, Antoniou SA, Schredl P, *et al*. Pepsin and oropharyngeal pH monitoring to diagnose patients with laryngopharyngeal reflux. *Laryngoscope* 2020;130(7):1780-1786.

13 Magliulo G, Plateroti R, Plateroti AM. Gastroesophageal reflux disease and the presence of pepsin in the tears. *Med Hypotheses* 2013;80(2):129-130.

14 Iannella G, Di Nardo G, Plateroti R, *et al*. Investigation of pepsin in tears of children with laryngopharyngeal reflux disease. *Int J Pediatr Otorhinolaryngol* 2015;79(12):2312-2315.

15 Batioglu-Karaaltin A, Saatci O, Akpinar M, Celik MO, Develioglu O, Yigit O, Külekçi M, Akarsubaşı AT. Helicobacter pylori in lacrimal secretions. *Ear Nose Throat J* 2016;95(3):E8-E11.

16 Bonini S, Labetoulle M, Messmer E, *et al*. Association of dry eye with laryngopharyngeal reflux in clinical practice. *Curr Eye Res* 2022;47(2):214-219.

17 Damiani V, Schindler A, Luccarelli V, Ciprandi G. Laryngopharyngeal reflux and eye: more than a hypothesis. *Eur J Rhinol Allergy* 2023;6(1):1-4.

18 Clayton JA. Dry eye. *N Engl J Med* 2018;378(23):2212-2223.

19 Balestrazzi A, Passali GC, Passali D, *et al*. A new therapeutic approach for the Dry Eye Syndrome in patients with laryngopharyngeal reflux: first data. *Acta Bio Med* 2020;91(1-S):36-42.

20 Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. *Cornea* 2003; 22(7):640-650.

21 Chun YS, Park IK. Reliability of 4 clinical grading systems for corneal staining. *Am J Ophthalmol* 2014;157(5):1097-1102.

22 Schaumberg DA, Gulati A, Mathers WD, Clinch T, Lemp MA, Nelson JD, Foulks GN, Dana R. Development and validation of a short global dry eye symptom index. *Ocul Surf* 2007;5(1):50-57.

23 Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). *J Voice* 2002;16(2):274-277.

24 Stevens S. Schirmer's test. *Community Eye Heath* 2011;24(76):45.

25 Zemanová M. Dry eye disease. a review. *Cesk Slov Oftalmol*

2021;77(3):107-119.

26 Qian LJ, Wei W. Identified risk factors for dry eye syndrome: a systematic review and meta-analysis. *PLoS One* 2022;17(8):e0271267.

27 Huang RJ, Su CY, Fang LJ, Lu JQ, Chen JS, Ding Y. Dry eye syndrome: comprehensive etiologies and recent clinical trials. *Int Ophthalmol* 2022;42(10):3253-3272.

28 Bron AJ, de Paiva CS, Chauhan SK, *et al*. TFOS DEWS II pathophysiology report. *Ocul Surf* 2017;15(3):438-510.

29 Mengher LS, Bron AJ, Tonge SR, Gilbert DJ. A non-invasive instrument for clinical assessment of the pre-corneal tear film stability. *Curr Eye Res* 1985;4(1):1-7.

30 Katz PO, Dunbar KB, Schnoll-Sussman FH, *et al*. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2022;117(1):27-56.

31 Davies I, Burman-Roy S, Murphy MS, Guideline Development Group. Gastro-oesophageal reflux disease in children: nice guidance. *BMJ* 2015;350:g7703.

32 Higuera-de-la-Tijera F. Efficacy of omeprazole/sodium bicarbonate treatment in gastroesophageal reflux disease: a systematic review. *Medwave* 2018;18(2):e7179.

33 Ummarino D, Miele E, Martinelli M, *et al*. Effect of magnesium alginate plus simethicone on gastroesophageal reflux in infants. *J Pediatr Gastroenterol Nutr* 2015;60(2):230-235.

34 Buckley RJ. Assessment and management of dry eye disease. *Eye (Lond)* 2018;32(2):200-203.

35 Gelardi M, Taliente S, Fiorella ML, *et al*. Ancillary therapy of intranasal T-LysYal® for patients with allergic, non-allergic, and mixed rhinitis. *J Biol Regul Homeost Agents* 2016;30(1):255-262.

36 Wan LQ, Jiang J, Arnold DE, Guo XE, Lu HH, Mow VC. Calcium concentration effects on the mechanical and biochemical properties of chondrocyte-alginate constructs. *Cel Mol Bioeng* 2008;1(1):93-102.

37 Strugala V, Kennington EJ, Campbell RJ, Skjåk-Bræk G, Dettmar PW. Inhibition of pepsin activity by alginates *in vitro* and the effect of epimerization. *Int J Pharm* 2005;304(1-2):40-50.

38 Tong T, Liu YJ, Kang JH, Zhang CM, Kang SG. Antioxidant activity and main chemical components of a novel fermented tea. *Molecules* 2019;24(16):2917.

39 Mills IJ. A person-centred approach to holistic assessment. *Prim Dent J* 2017;6(3):18-23.

40 Diaz-Vega B, Vitores-Mate S, Carpena-Torres C. Lid scrubbing with a gel combining natural extracts for dry eye treatment. *Int J Ophthalmol* 2023;16(7):1053-1059.

41 Jo YJ, Lee JS. Clinical efficacy of 0.05% cyclosporine nano-emulsion in the treatment of dry eye syndrome associated with meibomian gland dysfunction. *Int J Ophthalmol* 2022;15(12):1924-1931.

42 Eom Y. Clinical effectiveness of diquafosol ophthalmic solution 3% in Korean patients with dry eye disease: a multicenter prospective observational study. *Int J Ophthalmol* 2021;14(10):1518-1526.