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REVIEW PAPER

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Current recommendations for treatment and diagnosing of xerostomia in Sjögren's syndrome

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ABSTRACT

Introduction. Xerostomia is one of the most common and disturbing adverse effects of systemic diseases and their therapies. This complication markedly increases the risk for dental caries, difficulties with chewing, swallowing and sleep disorders with a significant impact on the patient's quality of life. Sjögren's syndrome (SS) is a systemic autoimmune disease that primarily affects the exocrine glands, resulting in dryness of the mouth due to lymphocytic infiltration of the salivary glands.

Aim. The aim of this paper is to present the current recommendations in diagnosing and treating SS-related xerostomia.

Material and methods. Analysis of literature

Results. For the assessment of SS-related xerostomia, only an unstimulated salivary flow with rates of 0.1 mL/min is included in the current SS classification criteria. Saxon test, sialography, ultrasonography of salivary glands play supporting function. Treatment of SS -related xerostomia includes an application of secretagogues and the implementation of specific dental prophylaxis measures. Adjuvant therapies include herbal remedies, photobiomodulation, and acupuncture.

Conclusion. Treatment of SS requires multidisciplinary care. There is no fully effective treatment of xerostomia that provides immediate and long-lasting results.

Keywords. saliva, Sjögren syndrome, xerostomia

Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by periductal mononuclear cell infiltrate in the salivary and lachrymal glands, autoimmunization, injuries to endothelial cells and their subsequent apoptosis. The periductal mononuclear cell infiltrates cause damage to glandular tissue in the salivary glands and results in decreased salivation. Typical features of SS are severe xerostomia and xerophthalmia, which are basic SS diagnostic criteria.[1-9] The presence of both dry mouth and dry eyes classified patients with 93% sensitivity and 97.7% specificity. The rate of dry mouth in SS ranges from 41% at initial diagnosis to 84% 10 years after diagnosis.[10] Diagnosis of primary SS, as approved in 2016 by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), is based on the weighted sum of 5 items.[11,12] According to this classification, an unstimulated salivary flow rate of 0.1 mL/minute in sialometry gives a score of 1 to the weighted sum of 5 items,

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according to the current EULAR/ACR criteria. Decreased salivation markedly affects oral health and very often inhibits normal functioning. Xerostomia is a severe medical problem. There is a 20% prevalence of dry mouth complaints of different origins in the general population.[7] The loss of saliva causes serious oral consequences, manifesting as an uncomfortable feeling of dry mouth and presenting numerous signs and symptoms mainly in the mucous membranes, lips, tongue, salivary glands and teeth.[9] The oral cavity deprived of saliva and its natural lubricative, protective and antibacterial properties is prone to a number of unfavourable consequences. It may include exacerbation of diseases affecting hard dental tissues and the periodontium, as well as a predisposition to opportunistic infections and pathologies of the oral mucosa. Dry mouth correlates with numerous clinical and psychosocial problems. Clinical problems are common in patients with hyposalivation and include rampant caries, gingival inflammations, fungal infections, rhagades, limited denture retention, or limitations in swallowing, eating, and speaking.[8] Moreover, xerostomia has a significant impact on the quality of life of patients who are affected.[1-5,13,14] Gaining knowledge about the causes, symptoms and treatment of xerostomia is very important and useful for both general practitioners and dentists.

Aim

The aim of this paper is to present the current recommendations in diagnosing and treating SS-related xerostomia.

Diagnosing of xerostomia

Typical saliva production has been measured at 0.5-1.5l per day in the healthy adult.[7] Percentage contributions of the different salivary glands during unstimulated flow are as follows: 20% from parotid, 65% from submandibular, 7% to 8% from sublingual, and less than 10% from numerous minor salivary glands. Stimulated high flow rates drastically change percentage contributions from each gland, with the parotid contributing more than 50% of total salivary secretions.[15] Stimulated saliva is produced in response to a mechanical, gustatory, olfactory, or pharmacological stimulus, contributing to around 40-50% of daily salivary production.[16,17]

There are different causes of dry mouth known so far, such as post radiation of head and neck cancer treatment and salivary gland hypofunction. Moreover, the common cause is the use of medications with potential xerostomic effects, mainly anticholinergic, sympathomimetic, sedative, hypnotics, opiates, antihistamines and muscle relaxants.[9] Decreased salivation gives similar clinical symptoms and can be detected by the same tests. However, in SS the detection of xerostomia is an integral part of a comprehensive, tentative diagnosis and SS confirmation. In SS, xerostomia is a part of the diagnosis, not only the consequence of disease. We need more precise and objective oral tests and procedures that can be used for the diagnosis and clinical decision making in SS. It has been recommended that unstimulated whole saliva measurement, the Saxon test, sialography, ultrasonic examination of salivary glands are useful for diagnosing SS-related xerostomia.[16]

Salivary flow measurement (sialometry) is widely applied in diagnosing xerostomia. Several methods for collecting saliva have been reported so far.[18] It is the most common, objective diagnostic test of xerostomia and it uses two parameters to assess saliva secretion: Salivary Flow (SF) index and Salivary Flow Rates (SFR). SF is a parameter allowing stimulated and unstimulated saliva flow to be classified as normal, low or very low (hyposalivation).[17] In adults, normal total stimulated SF ranges are 1–3 mL/minute, and low ranges are 0.7–1.0 mL/minute, while hyposalivation is characterized by a stimulated SF <0.7mL/minute.[17] SF index is a basic, cheap diagnostic tool, which may be available in every physician's office. SF and SFR can be used in both unstimulated and stimulated whole sialometry. Unstimulated sialometry is performed by the accumulation of saliva on the floor of the mouth, without swallowing for 60s. Then, the accumulated saliva is collected into a tube graded in millilitres (mL) with the aid of a laboratory glass funnel. It is repeated 4 more times for a total of 5min. Stimulated sialometry is performed by stimulation with 2% citrate solution to the dorsolateral borders of the tongue, with a cotton tipped applicator, 5 times over 2 min (0, 30, 60, 90, and 120s). Next, all the retained citrate solution in the mouth are eliminated. The steps of saliva collection and SFR assessment are the same as for unstimulated sialometry.[19] A more precise diagnostic test of SS-related xerostomia is an unstimulated whole sialometry, which lasts for 15 min. Unstimulated whole sialometry lasting for 15min is performed 2h after a meal using the standardized collection procedure. Saliva is collected in a graduated tube via a funnel every 2min. Volumes of up to ≤1.5mL/15min are marked as abnormal; volumes between 1.5 and 2.5mL/15min are marked as intermediate and volumes of ≥2.5mL/15min as normal. Volumes <2.5mL/min are considered abnormal and used for estimating sensitivity for correlation with all scintigraphic parameters.[20] According to the final classification criteria of SS, which was approved by the ACR and the EULAR in 2016, an unstimulated salivary flow rate of 0.1 ml/minute gives a score of 1 to the weighted sum of 5 diagnostic items. Moreover, sialometry can be divided into the whole saliva technique, which is the combined secretion of all salivary glands, and into the collection directly from a specific salivary gland. The reduced rate of secretion of unstimulated whole saliva has the highest diagnostic value in SS. On

the other hand, many changes in flow rate, not seen or less obvious when using whole saliva, have been reported in patients with SS tested with the separate glandular saliva technique. Differences in separate saliva secretion from major salivary glands in SS can depend on the severity and time of the disease. Among the salivary glands, in patients with SS, the parotid is the last one that is affected. Separate saliva collection by sialometry is considered a valuable diagnostic test.[21]

Another useful diagnostic method for xerostomia is the Saxon test. This test can complement stimulated whole sialometry and can be used for patients wearing dentures who are unable to masticate. It is implemented by chewing a folded sterile gauze sponge for 2 minutes and collecting the stimulated whole saliva. Salivation is quantitated by weighing the sponge before and after chewing. Normal control subjects produce ≤2.75 gm of saliva in 2 minutes. The Saxon test is a simple, reproducible and low-cost test for xerostomia and is treated as an equivalent of Schirmer's test in the labial glands.[22] This method can be modified by the different time of saliva collection and the use of different sizes of gauge sponge. In addition to measuring saliva collection, there are a few supplementary methods for quantitative analysis of salivary gland secretion function in SS. Commonly used imaging tests that will facilitate the diagnosis of xerostomia include radiograph sialography, salivary scintigraphy and various magnetic resonance imaging (MRI) techniques. They are mainly performed for the examination of the parotid glands. Major salivary glands scintigraphy is a nuclear imaging technique that through radioactive tracer infusion (Technethium-99 pertechnetate) permits to study glandular function by evaluating the distribution and speed of elimination of the radio-tracer after a secretive stimulation. Positive scintigraphy is defined as a test characterized by delayed uptake, reduced concentration and/or delayed secretion of the trace. The specificity and sensitivity of salivary gland scintigraphy are described as around 50% and up to 89%, respectively. Salivary gland scintigraphy is not a part of the recent classification criteria for SS. However, it is possible that this technique, monitoring salivary gland functioning over time, might still have some potential indications during patients' follow-up to objectively evaluate changes in their secretory function after treatment. Sialography is a traditional radiographic exam based on the cannulation of the main salivary ducts and the subsequent injection of an iodinated contrast medium, allowing the visualization of the architecture of the entire ductal system of the major salivary glands. Although sialography is considered a reliable and accepted method for SS diagnosis, it has limitations in terms of invasiveness and radiation exposure. In the current recommendation, the conventional techniques of radiograph sialography and salivary scintigraphy are replaced by various techniques of MRI and MR sialography. MRI is non-invasive, radiation-free, and sensitive to the morphological and signal changes of the parotid glands, and MR sialography is widely used to evaluate the parotid ductal system without using any exogenous contrast agent. Salivary gland scintigraphy is a safe and sensitive method for assessing the functions of salivary glands. Furthermore, not only the location and morphology of salivary glands can be obtained, but quantitative parameters can also be calculated. MRI is a technique that provides high-resolution images of the parotid glands, as well as great internal contrast of the parotid gland ducts and acinus, due to its high sensitivity to the protons in saliva. Two-dimensional (2D) sequences have been applied in the functional evaluation of the parotid glands. Furthermore, three-dimensional (3D) MRI is a potential modality for both the functional evaluation and morphological imaging of the salivary glands. The secretion function of the parotid glands can be assessed successfully in dynamic MR sialography by the time-dependent volume change ratio curve of the parotid gland duct. Compared with healthy volunteers, SS patients demonstrate a slower and more subtle curve of time-dependent volume change ratio, resulting in a significantly lower $slope_{1st}$ value, peak value, and total saliva secretion post-stimulation. In this method, the $slope_{1st}$ can be used as a quantitative indicator to differentiate normal salivary secretion in healthy people and salivary hypofunction in SS patients.[23,24]

Salivary gland ultrasonography (SGUS) plays a supporting role in the diagnosis of SS-related xerostomia. Salivary glandular damage is the cause of dryness in SS patients, and ultrasonographic imaging of the amount of glandular damage could be essential for evaluating the xerostomia. In SS, the damage could be found particularly in glandular tissues, mainly in the salivary glands, and fibrosis is the most common consequence of tissue damage. The list of parameters explored in SGUS includes echogenicity, homogeneity, number of hypo or anechoic areas, measurement of the biggest hypo or anechoic area, location of the hypoechoic areas in the gland, calcification, posterior border and measurement of the gland.

Among the tests presented for the assessment of SS-related xerostomia, only an unstimulated salivary flow with rates of 01mL/min is included in the current SS classification criteria. Other methods play an additional supporting function and can be used for detection xerostomia induced by other factors.

Treatment of patient with dry mouth

Treatment of xerostomia in SS is difficult. It is an autoimmune disease with systemic manifestations, thus a multidisciplinary management team has been recommended.[25] Treatment of xerostomia includes the resto-

ration or stimulation of saliva secretion and reduction of harmful symptoms of decreased salivation. There are different therapeutic methods to restore the lost functions, alleviating symptoms, preventing and correcting the possible consequences of the lack of natural saliva. They can be divided into endogenous and exogenous approaches. The endogenous approach involves the replacement or enhancement of the salivary gland function through pharmaceutical or genetic modifications and mechanical stimulation. Typically, such modifications are intended to stimulate the secretion of water, electrolytes as well as macromolecules, or preventive protection against harmful factors. The exogenous approach involves the topical application of saliva substitutes to replace lost or enhance the existing function of natural saliva, drinking water and the application of moisturizing preparations. Although there are various pharmaceutical compositions for managing the xerostomia, there is currently no fully effective treatment that provides immediate and long-lasting results.[25] General measures such as air humidification of the environment, namely of the bedroom, caries prevention and smoking cessation play an important role.[26] Frequent sips of oral solutions can be helpful, with options ranging from water to artificial saliva.[27] In SS, recent advances in how to assess changes in disease progression and activity objectively (via repeated biopsies of salivary glands, sialometry, sialochemistry, biomarkers, secretion and composition of tears, EULAR Sjögren's Syndrome Disease Activity Index: ESSDAI) and subjectively (EULAR Sjögren's Syndrome Patient Related Index: ESSPRI) have opened new ways to reliably assess the outcome of a particular treatment, although some final validation studies have to be completed before these tools can be generally applied in primary SS.[25] When looking at more organ-specific tools, sialometry, sialochemistry, ultrasound and repeated biopsies are proper tools to assess salivary gland functioning and regeneration.[25]

Endogenous approaches

Current first-line treatment in SS-related xerostomia is an application of secretagogues that promote the secretion of saliva. In patients with moderate-to-severe oral dryness and with residual salivary gland function, oral muscarinic agonists, such as pilocarpine or cevimeline, are the treatment of choice in the absence of contraindications.[26] Commonly reported adverse effects include sweating, warmth and flushing sensation, increased urinary frequency, headache, blurred vision, diarrhea and abdominal discomfort.[26,28] Moreover, these drugs are often contraindicated in patients with cardiac or respiratory disorders, so use is mainly restricted to patients with severe dry mouth due to SS.[28] Pilocarpine is a parasympathomimetic agent that functions primarily as a muscarinic agonist with mild β-adrenergic activity.[29] This alkaloid causes pharmacologic stimulation of exocrine glands in humans, resulting in diaphoresis, salivation, lacrimation, and gastric and pancreatic secretion.[29] The low doses of pilocarpine sodium alginate improve intraoral xerostomic conditions and quality of everyday life in SS patients with dry mouth through increasing saliva secretion.[16,29] Pilocarpine is prescribed for its acute and short-term effect on inducing salivary fluid secretion. Long-term pilocarpine administration in patients with xerostomia is effective for restoring salivary flow and relieving symptoms. This suggests that, in addition to its transient effect on stimulating salivary secretion, pilocarpine has long-lasting beneficial activity against salivary gland dysfunction. However, the underlying mechanism of this potential beneficial effect is not understood.[30] The patients usually receive 5 mg of pilocarpine hydrochloride three times a day and assuming a patient's weight of 60kg, the dose will be 8.3μg/100g, but the pilocarpine dose used in the long-lasting therapy is approximately 10 times higher than that used clinically in short-lasting therapy.[30] Another recommended secretagogue is cevimeline. Although the clinical practice guideline committee recommends the use of cevimeline to improve salivary secretion, to reduce dry mouth, and oral mucosal abnormalities, cevimeline can induce adverse events.[16] However, there are no reports assessing its use in long-lasting therapy.

Biological treatment

A small number of biological therapies have been tried in primary SS with mixed successes. The preliminary data on rituximab and eprattuzumab are promising, but the efficacy of IFN-α is unclear and TNF-α blockade has been shown ineffective.[31] Xerostomia in SS is not an indication for biological treatment, but the effectiveness of this therapy can reduce the severity of xerostomia.

Several other biological therapies targeting other immune pathways relevant to primary SS pathogenesis may also be useful, such as agents targeting T-cells, IFN-α, IL-6 and other cytokines, co-stimulation/adhesion molecules, B-cell growth factors and Toll-like receptors (TLRs).[31]

Clinical trials of other biological therapies in SS are warranted, but the appropriate outcome measures and patient selection for such clinical studies must be carefully considered when designing the clinical trials.[31]

Adjuvant therapies and adjuvant medical support

Xerostomia can be modified by accompanying systemic diseases and drugs. Pharmacological treatment of both xerostomia and systemic diseases requires the modification of doses of the drugs, the time of the drug application and the choice of the type of drugs in order not to worsen the symptoms of dry mouth. Moreover, ad-

juvant therapy and medical support can be used. These new therapies and preventive methods for dry mouth include antioxidants. It has been suggested that oxidative stress is one of the causes of age-related diseases. Ubiquinol has antioxidant activity and also stimulates ATP production, suggesting that promotion of saliva secretion by ubiquinol in previous studies may have been attributable to these two effects. Ubiquinol is synthesized by humans, but its production has been shown to decrease with aging, and this decrease in ubiquinol is possibly associated with reduced secretion of saliva.[29] Therefore, it is possible that maintaining a higher ubiquinol level after middle age might prevent dry mouth.[30] It has been suggested that tissue damage due to oxidative stress caused by oxygen radicals directly impairs salivary gland function, so protection against oxidative damage may be important for maintaining adequate production of saliva. Some randomized control trials showed thyme honey's positive effects on the management of xerostomia.[25] They also provided evidence that better management of xerostomia can improve patients' quality of life.[25] A diet rich in antioxidants reduces the consequences of xerostomia. Despite its limitations, randomized control trial showed thyme honey's positive effects on the management of radiation-induced xerostomia in head and neck cancer patients.[25] It also provided evidence that the better management of xerostomia can improve patients' quality of life.[25] Some randomized control trials showed thyme honey's positive effects on the management of xerostomia in head and neck cancer patients.[25]

Some research showed a significant increase in salivary flow rate after treatment with herbals.[16] Herbal medicines potentially improve salivary function and reduce the severity of dry mouth in cancer patients, and they are relatively safe. The most common single herbs used for SS are Scrophularia ningpoensis, Ophiopogon japonicus, raw Rehmannia glutinosa, Trichosanthes kirilowii, Scutellaria baicalensis, Lycium barbarum, Rheum tanguticum, Chrysanthemum morifolium, Salvia miltiorrhiza and Dendrobium chrysanthum. They can be administered in a single prescription or in combinations of formulae, usually in patterns for two and three herbals.[32] These items may have effects on antioxidant capacity, anti-inflammatory function and dry eye or dry month improvement. Furthermore, they have an immune modulation or a tissue fibrosis alleviation function. However, methodological limitations and a relatively small sample size reduce the strength of the evidence of their effectiveness. In the future, more high-quality trials reporting sufficient methodological data, more clinically homogenous trials and further evidence of safety are warranted to draw definitive conclusions concerning the effectiveness of herbal medicines.[33] Zeng Ye decoction is extracted from figwort, Ophiopogon japonicus and Rehmannia glutinosa Libosch. The Zeng Ye decoction consists of 30g figwort, 24g Ophiopogon japonicas and 24g Rehmannia glutinosa Libosch, decocted for ~30min to produce the solution of 1g raw herbs per 1ml decoction. In the field of traditional Chinese medicine, Zeng Ye decoction, as an important Chinese medicinal agent, is widely used for relieving constipation due to body fluid deficiency. The potentially effectiveness of this agent is based on the theory of 'increasing body fluid for curing constipation', which was proposed by the famous medical scholar JuTong Wu with regard to epidemic febrile diseases.[34] Zeng Ye decoction has a significant curative effect on SS via upregulation of the levels of aquaporin-1 and -5. The high yield of these water channel proteins in the salivary glands facilitates the secretion of fluid, and is beneficial to recovery from SS. This result may be associated with the different immune mechanisms of the different ingredients of Zeng Ye decoction in the early development of SS. Another recommended Chinese herbal composition is a combination of Radix Pseudostellariae 30g, Radices Paeoniae Alba 12g, Schisandrae Chinensis Fructus 10g, Fructus Ligustri Lucidi 15g, Polygonatum SibiricumRed 15g, Smoked Plums 12g, Fructus Mori 15g, Glabrous Sarcandra Herb 15g, Rhodiola Sachalinesis15g, Artemisia Apiacea 15g. The Chinese medicine decoction is given in two packs a day. This composition has the effect of nourishing, supplementing and activating the blood. The two packs are given after breakfast and lunch respectively and the course of treatment usually lasts for 3 months.[34] Chinese herbal medicine for nourishing, supplementing and activating blood can alleviate the disease activity of SS by regulating the immune balance of Th1/Th2.[35,36,37]

Furthermore, some non-pharmacological therapies can be very helpful in treating xerostomia. They improve the quality of life and reduce the consequences of decreased salivation. Acupuncture as part of therapy for xerostomia can improve patients' subjective symptoms. A study evaluating the preventive effect of acupuncture for xerostomia showed positive changes in both unstimulated and stimulated salivary flow rates and dry mouth related symptoms. Acupuncture treatment is well tolerated by all patients and no severe adverse effects are seen.[38] Another non-pharmacological treatment of xerostomia is photobiomodulation. Photobiomodulation therapy is defined as a form of light therapy.[39] Visible, infrared and near-infrared light is absorbed by endogenous chromophores, triggering biological reactions that are not thermal or cytotoxic, through photochemical or photophysical events, leading to physiological changes.[39] Photobiomodulation supports the physiological function of salivary glands. There are few reports regarding the effectiveness of this therapy and possible side-effects. However, treatment of xerostomia is extremely

difficult in patients who wear dentures. Dentures may exacerbate symptoms of xerostomia. Moreover, denture stabilization is limited. Wearing removable dentures in worse salivary conditions can promote oral lesions formation. On the other hand, dentures can be used in the treatment of xerostomia. Some modified removable dentures were described in the therapy of xerostomia, and a removable dental denture was fabricated with inbuilt sensors to help in the management of xerostomia.[39] A micropressure sensor is incorporated into the prosthesis to detect dry mouth. On detecting a dry mouth, tongue pressure ejects artificial saliva from a capsule inside the sensor. The addition of a small sensing unit helps detect dry mouth. A saliva substitute is released according to the patient's requirements and unnecessary dispensing and frequent replacement of artificial saliva is avoided.[40]

Oral moisturizing agents

Oral moisturizing agents can improve dry mouth and oral mucosa abnormalities, and has virtually no side effects. However, oral moisturizing gel and artificial saliva have adverse events related to digestive symptoms.[16] Moreover, it has been shown in the literature that some oral moisturizers may have erosive potential due to their acidic pH, which is below the critical pH of dentin and enamel.[38] Clinicians should therefore be aware of this erosive potential of the products and make recommendations to manufacturers for future formulations avoiding acidic pH.[41] For this reason, care should be taken to formulate products with safe pH values for both enamel and root dentin which, based on the specific formulation, should be around 6.7 or higher.[41] Recent studies have concluded that there is great variation in the pH values among the most common oral moisturizers on the market and that there is a strong correlation between the pH values and the erosive potential of these products.[38] Thus it would seem reasonable for practitioners to take care in recommending oral moisturizing agents with a safe formulation for their patients.[41,42] Saliva substitutes, lubricating agents and mechanical stimulation by chewing sugar-free gum are usually employed in patients with mild hyposialia.[26] Topical fluoride and fluoride toothpaste to prevent caries are also strongly recommended.[26] A multicenter randomized controlled trial has shown that mild intraoral electrostimulation can alleviate oral dryness and had no adverse effects.[26,42,43]

Prophylaxis

In every case of xerostomia, the mechanism of oral dryness should be individually determined, since there are different ways to prevent sicca symptoms. It may be possible to keep to the strategy of limited intake of certain kinds of medicine during the treatment of other conditions or switching to another drug that does not cause oral dryness, if this is possible. Those measures may include salivary gland protectors, such as amifostine, hyperbaric oxygen and the use of intraoral stents during head and neck cancer radiotherapy.[5,33,42,43] In terms of SS, we have not found many prevention mechanisms, due to its complexity as an autoimmune disorder. Moreover, at present the only thing that a person diagnosed with this disease can do is to reduce the severity of the condition. As stated above, patients with SS must be observed by a multidisciplinary team and such conditions as malignant lymphoma (the features of which should be noted in diagnosis or other serious complications, including hematological malignancies, liver diseases and cardiovascular disease) can negatively affect the prognosis of patients with SS.[16]

Conclusions

To sum up, we have to conclude that nowadays there are a lot of different ways to manage xerostomia or sicca manifestations of SS. Some of these are limited (hydroxychloroquine, herbal medicine) and more randomized control trials need to be conducted to prove their effectiveness. In the systemic treatment of SS, promising results have been shown by some biological therapies and oral muscarinic agonists in improving dry mouth abnormality. However, one must remember that as of today, there is no fully effective treatment of xerostomia that provides immediate and long-lasting results.

There is currently no cure for SS that can restore gland secretion, although with recent advances in treatment modalities, there is a hope that the management of this autoimmune disease will soon improve. Moreover, in the treatment of patients with xerostomia, due to causes other than SS, careful evaluation is important to define the cause and appropriate treatment.

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