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An update of the etiology and management of xerostomia

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Salivary gland disease gives rise to salivary gland enlargement, pain, and prolonged xerostomia (dry mouth). Xerostomia is the most common long-standing problem for the majority of affected patients. There are many causes of dry mouth, with long-standing xerostomia being a particular problem in Sjögren's syndrome and after radiation to the head and neck region. Xerostomia is usually managed with saliva substitutes, but a large number of potential systemic therapies of long-standing xerostomia now exist. Some—particularly immunosuppressants—are of fundamental interest for the potential reduction of gland damage in Sjögren's syndrome but as yet are of limited clinical usefulness. Others, particularly pilocarpine and cevimeline, are, or have the potential to be, clinically useful in stimulating salivation by virtue of their action on cholinergic receptors. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;97:28-46)**

Xerostomia, or dry mouth, is the abnormal reduction of saliva and can be a symptom of certain diseases or be an adverse effect of certain medications. The causes of xerostomia include diseases of the salivary glands such as Sjögren's syndrome (SS), uncontrolled diabetes mellitus, radiation to the head and neck region, chemotherapy (Table I), and a number of commonly used medications (Table II). Injury to the head or neck can damage the nerves that are essential for the production and secretion of saliva by the salivary glands. Occasionally, xerostomia may be subjective, with no evidence of altered salivary flow. In these patients, xerostomia is often associated with psychological factors.[1]

The average person produces at least 500 mL of

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Table I. Causes of long-standing xerostomia

Iatrogenic
Drugs
Local radiation
Chemotherapy
Chronic graft-versus-host disease
Diseases of the salivary glands
Sjögren's syndrome
Sarcoidosis
HIV disease
Hepatitis C virus infection
Primary biliary cirrhosis
Cystic fibrosis
Diabetes mellitus
Others
Rare causes
Amyloidosis
Hemochromatosis
Wegener's disease
Salivary gland agenesis (with or without ectodermal dysplasia)
Triple A syndrome
Others

saliva over a 24-hour period. Salivary flow rates vary considerably during any one 24-hour period depending on the demand or the current physiologic status of the patient. The unstimulated/resting flow rate is 0.3 mL/min, whereas the flow rate during sleep is 0.1 mL/min; during eating or chewing, it increases to 4.0 to 5.0

Table II. Drugs that may give rise to xerostomia

Drugs with anticholinergic effects
    Atropine and analogs (antimuscarinics)
    Tricyclic antidepressants
    Serotonin reuptake inhibitors
    Antihistamines
    Antiemetics
    Antipsychotics
Drugs with sympathomimetic actions
    Decongestants
    Bronchodilators
    Appetite suppressants
    Amphetamines
Other drugs
    Lithium
    Omeprazole
    Oxybutynin
    Disopyramide
    Dideoxyinosine
    Didanosine
    Diuretics
    Protease inhibitors

mL/min. In human beings, saliva is always hypotonic to plasma, with sodium and chloride ion concentrations being less than those of plasma. The greater the secretory flow rate, the higher the tonicity of the saliva. Salivary gland secretion is mainly under autonomic nervous control, but various hormones may also modulate salivary composition. Secretion appears to be dependent on several modulatory influences that act either through a cyclic adenosine monophosphate–dependent or a calcium-dependent pathway.

Saliva consists of 2 components that are secreted by independent mechanisms: First, a fluid component that includes ions, produced mainly by parasympathetic stimulation; second, a protein component arising from secretory vesicles in acini and released mainly in response to sympathetic stimulation. Excitation of either sympathetic or parasympathetic nerves to the salivary glands stimulates salivary secretion, but the effects of the parasympathetic nerves are stronger and longer-lasting.

The ducts of salivary glands respond to both cholinergic and adrenergic agonists by increasing the rates of secretion of potassium (K^+) and bicarbonate (HCO_3^-). In serous acinar cells, acetylcholine, norepinephrine, substance P, and vasoactive intestinal polypeptide are released by specific nerve terminals and increase the secretion of salivary amylase and the flow of saliva. Acetylcholine, substance P, and norepinephrine acting on α-receptors increase the concentration of calcium ions in the serous acinar cells, resulting in profuse secretion with a lower concentration of amylase. In contrast, norepineph-

rine acting on β-receptors and vasoactive intestinal polypeptide elevates the cyclic adenosine monophosphate concentration in acinar cells, eliciting a secretion that is rich in amylase.[2]

Thus, parasympathetic stimulation produces copious saliva of low protein concentration, whereas sympathetic stimulation produces little saliva but with high protein concentration, which may give a sensation of dryness.[3]

THE ETIOLOGY OF LONG-STANDING XEROSTOMIA

Long-standing xerostomia (dry mouth) has many causes,[4] but drug-induced xerostomia is the most common type.

Iatrogenic

Drugs. Xerostomia is the most common adverse drug-related effect in the oral cavity. To date, xerostomia has been associated with more than 500 medications. In addition, the synergistic effects of medications have been recognized and are increasingly common in elderly patients taking multiple medications.[5] Dry mouth is a common problem for many elderly persons.[6]

The principal mechanism of drug-induced xerostomia is an anticholinergic or sympathomimetic action; thus, the drugs most commonly implicated in xerostomia include tricyclic antidepressants, antipsychotics, benzodiazepines, atropinics, β-blockers, and antihistamines. Therefore, xerostomia is common in patients treated for hypertensive or mental illness. A wide range of other drugs can give rise to oral dryness (Table II).[4] Often promoted as having fewer anticholinergic actions than the tricyclics, the serotonin reuptake inhibitors also cause some degree of xerostomia. Some other newer therapies, including omeprazole, anti–human immunodeficiency virus (HIV) protease inhibitors, the nucleoside analog HIV reverse transcriptase inhibitor didanosine, trospium chloride, elliptinium, tramadol, and new-generation antihistamines may all cause drug-induced xerostomia.[5-16]

Some drugs—such as hydralazine, busulfan, quinidine sulfate, and thiabendazole—can give rise to primary Sjögren's syndrome–like disease; however, this clinical disease can be transient. In addition, affected patients may not have high levels of immunologic markers of Sjögren's syndrome; thus, it seems unlikely that this is true Sjögren's syndrome.[17]

Therefore, with drug-associated xerostomia, there is usually a fairly close temporal relationship between the commencement of medication or increasing the dose and experiencing the dry mouth. However, the cause

for which the drug is being taken may also be important. For example, patients with anxiety or depressive conditions may even report dry mouth in the absence of drug therapy.

Radiation. Salivary tissue is highly vulnerable to radiation damage, with the parotid glands being most readily damaged.[18,19] A radiation dose as low as 20 Gy can cause permanent cessation of salivary flow if given as a single dose. At doses above 52 Gy, salivary dysfunction is severe. Treatment of oral carcinoma conventionally involves the administration of a dose of 60 Gy to 70 Gy, and this can lead to a rapid decrease in flow during the first week of radiation, with an eventual reduction of 95% in the region. By 5 weeks of radiation, the flow virtually ceases and rarely recovers completely. Both resting and stimulated salivary flow are inhibited. However, there is a compensatory hypertrophy of the unirradiated salivary glandular tissue after a few months and up to a year, leading to some lessening in the sensation of oral dryness, but beyond this time, little further improvement occurs. The degree of xerostomia depends on the degree of exposure of the salivary tissue to the radiation,[20] with partially irradiated glands having resultant higher flow rates than fully irradiated glands.

Mantle, unilateral, and bilateral fields of radiation can be associated with a reduction in salivary flow of 30% to 40%, 50% to 60%, and 80%, respectively. Radiation to a salivary tumor may avoid the contralateral gland and not cause severe xerostomia, whereas radiation to the nasopharynx damages both of the parotid glands, causing severe and permanent xerostomia. Radiation fields used in the treatment of oral cancer normally circumvent at least part of the parotid glands so that xerostomia may not be as severe.[18] Fortunately, the more recent cone radiation techniques restrict unwanted irradiation to one side alone, which preserves contralateral salivary function. Other sources of irradiation such as radioactive iodine used for treating thyroid disease may also cause salivary damage.[21]

Chemotherapy. Various malignancies are treated with chemotherapy or a combination of radiation and chemotherapy.[22] In a study of 127 patients with advanced cancer and xerostomia,[23] xerostomia was found to be the fourth most-common symptom reported (78% of patients) and the degree of xerostomia was related to the total number of chemotherapeutic drugs used. Xerostomia was ranked the third most-distressing symptom. The severity of xerostomia was correlated with the severity of oral discomfort, dysgeusia, dysphagia, and dysphonia. Drugs used to treat cancer can make saliva thicker, causing the mouth to feel dry.

Induction paclitaxel, carboplatin, and infusion 5-fluoruracil followed by concurrent radiation and weekly paclitaxel/carboplatin in the treatment of locally advanced head and neck cancer can frequently cause xerostomia.[24] Xerostomia was reported by 65% of 50 patients treated over 12 months with supradose selective intra-arterial cisplatin and concomitant standard radiation for inoperable stage IV head and neck squamous cell carcinoma.[25] In vitro chemotherapeutic cytokines cause a pronounced inhibitory effect on the human salivary cell line.[26]

Chronic graft-versus-host disease. Xerostomia is a well-known complication of chronic graft-versus-host disease (cGVHD).[27-32] A prolonged significant reduction in parotid salivary flow rate correlates with the histopathologic findings (ie, fibrosis of glands) and alterations in the chemical composition of saliva (ie, a reduced sodium Na+ and raised K^+ ion concentration).[28] The squamous epithelium of the oral mucosa and the epithelium of salivary glands are affected early in the course of cGVHD,[32] but the major salivary functional injury in cGVHD occurs later, with the target of destruction possibly being the muscarinic receptor, water transporter, or calcium ions.[28]

Disorders of the salivary glands

Sjögren's syndrome. Sjögren's syndrome[33] (SS) is a chronic multisystem immune-mediated disorder characterized by inflammation of exocrine glands leading to clinical symptoms of dryness, particularly of the eyes and mouth, which can be severe and disabling.[34] It can be classified as *primary disease*, of which there are only symptoms and signs affecting the eyes and mouth or *secondary SS*, in which there is xerostomia, xerophthalmia, and an associated connective tissue disorder—most frequently rheumatoid arthritis or systemic lupus erythematosus (SLE). Primary SS is often associated with B-cell hyperreactivity manifested by hypergam-

Table III. Clinical manifestations of SS

Fatigue; normocytic anemia
Sicca complex — dry eyes and dry mouth
Rheumatoid arthritis or other connective tissue disease
Salivary gland enlargement
Purpura (nonthrombocytopenic); hyperglobulinemia; and vasculitis
Renal tubular acidosis or other tubular disorders
Polymyopathy and neuropathy
Central nervous system disease
Chronic liver disease
Chronic pulmonary disease
Lymphoma — local or generalized
Cryoglobulinemia; macroglobulinemia

SS, Sjögren's syndrome.

Table IV. Classification of SS[35]

I. Ocular symptoms—A positive response to at least 1 of the following questions:
    1. Have you had daily, persistent, troublesome dry eyes for more than 3 mo?
    2. Do you have a recurrent sensation of sand or gravel in the eyes?
    3. Do you use tear substitutes more than 3 times a day?
II. Oral symptoms—A positive response to at least 1 of the following questions:
    1. Have you had a daily feeling of dry mouth for more than 3 mo?
    2. Have you had recurrently or persistently swollen salivary glands as an adult?
    3. Do you frequently drink liquids to aid in swallowing dry food?
III. Ocular signs (—ie, Objective evidence of ocular involvement defined as a positive result for at least 1 of the 2 following two tests):
    1. Shirmer's test, performed without anesthesia (≤5 mm in 5 min)
    2. Rose bengal score or other ocular dye score (≥4 according to van Bijsterveld's scoring system).
IV. Histopathology—In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an
    expert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are ad jacent to normal-appearing
    mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue.
V. Salivary gland involvement—Objective evidence of salivary gland involvement defined by a positive result for at least 1 of the following
    diagnostic tests:
    1. Unstimulated whole salivary flow (<1.5 mL in 15 min)
    2. Parotid sailography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of
    obstruction in the major ducts.
    3. Salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer.
VI. Autoantibodies—Presence of 1 or both of the following autoantibodies in the sera:
    1. Antibodies to Ro (SSA) antigens.
    2. Antibodies to La (SSB) antigens.
Revised rules for classification
    For primary SS
      In patients without any potentially associated disease, primary SS may be defined as follows:
        a. The presence of any 4 of the 6 abovementioned items is indicative of primary SS, as long as either item IV or VI yields positive
        results.
        b. The presence of any 3 of the 4 following objective criteria: III, IV, V, or VI
        c. The classification procedure represents a valid alternative method for classification, although it should be more properly used in a
        clinical-epidemiologic survey.
    For secondary SS
      In patients with a potentially associated disease (for instance, another well-defined connective tissue disease), the presence of item I or
      item II plus any 2 from among items III, IV, and V may be considered indicative of secondary SS.
    Exclusive criteria
      Past head and neck radiation treatment
      Hepatitis C infection
      Acquired immunodeficiency syndrome
      Pre-existing lymphoma
      Sarcoidosis
      Graft-versus-host disease
      Use of anticholinergic drugs (for a time shorter than the 4-fold life of the drug)

SS, Sjögren's syndrome.

maglobulinemia and anti-Ro or anti-La autoantibodies, or both. The classification is possibly somewhat simplistic because many patients with primary SS have a spectrum of other systemic, and often autoimmune, disorders.[35]

SS is the second most-common autoimmune connective tissue disorder, and symptoms of xerostomia and xerophthalmia are caused by profound lymphocytic infiltration into the salivary and lacrimal glands.[33] The clinical manifestations of SS are outlined in Table III.

The recently modified internationally agreed-on criteria may be applied (Table IV) for the diagnosis of SS.[35] In addition to the subjective xerostomia symptoms of dry eyes and dry mouth, the following objective items should be fulfilled: (1) ocular signs by Schirmer's test or rose bengal dye score, or both; (2) focal sialadenitis by histopathology; (3) salivary gland involvement by either salivary scintigraphy, parotid sialography, or unstimulated salivary flow; (4) autoantibodies of Ro/SSA and/or La/SSB specificity.[36] The problems of diagnosis are compounded by the finding of "positive" antinuclear antibodies in a high percentage of the general population. Nonspecific changes of sialadenitis are frequently confused with the focal lymphocytic infiltration characteristic of SS, especially if minor salivary gland biopsy specimens are examined by inexperienced observers. The distinction between patients with fibromyalgia

with low-titer antinuclear antibodies and those with primary SS remains a difficult one to make. Even in patients fulfilling strict criteria for SS, the genomic search for critical genes has proved difficult because of the multigenic pattern of inheritance and the strong role of currently undefined environmental factors.[37]

No single environmental factor has been detected in the majority of patients with SS. A possible viral etiology has long been suggested, and a number of potential viral triggers has been proposed, including Epstein-Barr virus, hepatitis C virus (HCV), and human retrovirus 5,[36] all of which have now been discounted as etiologically significant. The labial gland biopsy specimens of patients with marked oral and ocular dryness often reveal that they have almost 50% of their glandular cells intact.[38] The finding of serum autoantibodies directed against the muscarinic M3 receptor in patients with primary SS may be an important advance in understanding the pathogenesis not only of the impaired glandular function, but also the associated features of autonomic dysfunction in some patients.[36]

Sarcoidosis. Chronic sarcoidosis can give rise to xerostomia[40] and salivary gland enlargement in up to 9% of affected patients, often occurring as part of Heerfordt's syndrome.[41] In a recent study,[40] the degrees of xerostomia and xerophthalmia were similar among a group of patients with SS and a group with sarcoidosis, whereas parotid gland enlargement was more frequently found in those with sarcoidosis. Patients with sarcoidosis had mainly pulmonary and skin involvement, whereas those with SS presented more frequently with Raynaud's phenomenon. Relevant autoantibodies were, as expected, more often found in patients with SS than in individuals with sarcoidosis. The histopathologic findings from a minor salivary gland biopsy revealed noncaseating granulomas in 58% of patients with sarcoidosis, whereas in persons with SS, focal sialadenitis is the histologic picture. Pulmonary involvement is a determining factor in the differentiation of sarcoidosis from SS, as is the presence of elevated serum levels of angiotensin-converting enzyme and other clinical, radiologic, and serologic features of sarcoidosis.

HIV disease. Salivary gland disease can arise in 4% to 8% of adults and children with HIV infection. The principal clinical features of salivary gland disease in HIV infection are as follow: HIV salivary gland disease with associated xerostomia and salivary gland enlargement; Kaposi's sarcoma causing salivary gland enlargement; non-Hodgkin's lymphoma; intraglandular lymphadenopathy; and acute suppurative sialadenitis.[42-44]

HIV salivary gland disease (HIV-SGD) is a distinct disorder characterized by recurrent or persistent major salivary gland enlargement and xerostomia. The parotids are most frequently affected, often with profound bilateral enlargement. HIV-SGD affects up to 8% of adults (and may be more frequent in children) and has a worldwide distribution. Salivary gland disease tends to arise in late HIV infection, but it can occasionally be the first manifestation of HIV disease. A higher male-to-female ratio of involvement has been reported, but this probably reflects the epidemiology of the patients who have been reported. HIV salivary gland disease may be associated with HLA-DR5 and is part of a more generalized disorder termed *diffuse infiltrated lymphocytosis syndrome*, which is characterized by CD8$^+$ T-cell infiltration of the lungs, salivary glands, and lacrimal glands.[44,45]

The clinical picture of HIV-SGD mimics that of SS; however, there are distinct histopathologic and serologic differences between the 2 disorders. Patients with HIV-SGD generally do not have anti-Ro or anti-La antibodies. The minor salivary gland histopathology of HIV-SGD is generally similar to that of SS, in that it is dominated by perivascular, periacinar, and periductal lymphocytic infiltrates; however, the majority of the infiltrating T cells are CD8$^+$. Multicystic lymphoepithelial lesions may also occur, but cystic change can also arise from intraglandular ductal obstruction by hyperplastic lymphoid tissue.

Xerostomia independent of HIV-SGD may arise in HIV infection as a consequence of some nucleoside analog HIV reverse transcriptase inhibitors or protease inhibitors,[46,47] by an unknown mechanism. Didanosine induces xerostomia[48]; in fact, xerostomia may be seen in up to one third of patients taking it.[49] Up to 7% of patients using protease inhibitors may have xerostomia.[50]

HCV infection

Unlike the other hepatotropic hepatitis viruses, HCV frequently gives rise to a wide spectrum of extrahepatic manifestations that include salivary gland disease.[51,52] HCV-associated salivary gland disease arises in 10% to 33% of affected patients.[53] Xerostomia is the predominant symptom of HCV-associated salivary gland disease.[54,55] In a study by Henderson and colleagues,[56] the salivary flow rates were found to be significantly lower in patients with HCV infection than in previously reported healthy control subjects.

The histopathologic features of HCV-associated sialadenitis are similar—but not identical— to those of SS,[57] with a lesser degree of inflammation being found in HCV. Analysis of the lymphocytic focus has shown

Table V. Effects of long-standing xerostomia[88-90]

Increased frequency of caries (particularly cervical caries)
Proclivity toward acute gingivitis
Dysarthria
Dysphagia
Dysgeusia
Proclivity toward candidal infection (eg, acute pseudomembranous candidiasis, median rhomboid glossitis, denture-associated stomatitis, angular cheilitis)
Burning tongue/depapillation of tongue
Oral mucosal soreness
Dry, sore, cracked lips
Salivary gland enlargement (various causes)

that individuals infected with HCV have a predominance of CD20-positive cells.[58] HCV infection may occasionally give rise to non-Hodgkin's lymphoma and salivary disease akin to that of SS, but there is no real evidence to suggest that SS is related to HCV infection.[59]

Other viruses. Other viruses such as Epstein-Barr[60-62] have been implicated in xerostomia. A link with xerostomia and human T-lymphotropic virus 1 infection has also been found.[63,64] The incidence of hepatitis B, E, and G virus markers in patients with SS has been reported to be higher than that of healthy subjects,[65] but it seems unlikely that this is of any etiologic significance.

Other causes of xerostomia. Primary biliary cirrhosis,[66] cystic fibrosis,[67] and diabetes mellitus[68-79] rarely cause xerostomia, as do salivary gland agenesis,[80] with or without ectodermal dysplasia[81]; triple-A syndrome[82]; amyloidosis[83,84]; and hemochromatosis.[85,86]

CLINICAL CONSEQUENCES OF XEROSTOMIA

The clinical consequences of long-standing xerostomia are summarized in Table V. Xerostomia is unpleasant and, if prolonged, can lead to a reduced quality of life.[87-90]

The xerostomia of SS can be particularly troublesome, giving rise to dysarthria and dysphagia. Quality-of-life assessments have been used in some studies to evaluate the effects of xerostomia in patients with primary SS, wherein those with xerostomia have been shown to have a reduced quality of life compared with healthy persons.[91-93] However, studies incorporating a larger sample size are required to confirm these findings and a disease-specific measure is required to assess the impact of SS on health-related quality of life.[93]

INVESTIGATIONS OF PROLONGED XEROSTOMIA

The investigation of xerostomia centers upon a series of clinical, radiologic, and laboratory-based tests. Much can be elicited from the history and clinical examination alone, and on the basis of these and a knowledge of the possible causes of xerostomia, certain specific investigations can be undertaken to confirm the working diagnosis. The investigations can be grouped under the following headings: hematology, biochemistry, immunology, imaging, histology, and others (Table VI).

MANAGEMENT OF PROLONGED XEROSTOMIA

Assessments of available therapies of xerostomia has been difficult partly because of a lack of well-designed randomized, controlled clinical trials and partly because of disagreement until recently[35] over diagnostic criteria for such disorders as SS. Clinical trials of new therapies in disorders such as rheumatoid arthritis and SLE have been advanced by the development of internationally agreed-on assessment and outcome measures such as the American College of Rheumatology/European League Against Rheumatism core datasets of disease activity in rheumatoid arthritis and measures of activity and damage in SLE such as the British Isles Lupus Assessment Group, SLE Disease Activity Index, and SLE International Collaborating Clinics. No such equivalent consensus exists for SS or any other disorder giving rise to prolonged xerostomia, and, as a result, clinical trials have all used different, unvalidated, ad hoc measures of disease assessment and outcome. One attempt to bring a coherent approach to this issue is the "Copenhagen model," or disease assessment wheel, that places each disease manifestation within specific categories depending on their presumed pathogenesis.

Attempts have also been made to develop this into a severity tool by grading specific manifestations according to severity. In March 2000, interested specialists from around Europe met to develop a consensus on the broad principles underpinning disease assessment in SS (particularly primary SS).[34] It was agreed to adopt the international approach of dividing assessment into exocrine and nonexocrine disease activity (potentially reversible and including sicca symptoms and objective measures and systemic symptoms particularly fatigue and clinical features), damage (present for more than 6 months), health-related and generic quality of life, and standard approaches to adverse events/toxicity and health economic aspects. The workshop also began the process of developing specific measures of sicca symptoms, and systemic activity and damage. To convert this approach into detailed, experimentally validated assessment tools, a UK-based collaboration has fo-

Table VI. Range of Investigations for prolonged xerostomia[230-232]

Hematology	
Investigation	Comments
Hb	Anemia or chronic disease (SS).
MCV increased/vitamin B_{12} decreased	Pernicious anemia may be seen in patients with other autoimmune disease.
White blood cell count and differential	Abnormal in HIV, lymphoreticular tumor, primary SS, or SLE.
Platelets	Thrombocytopenia in HIV, primary SS, or SLE.
Biochemistry	
Investigation	Comments
Serum protein	↑ total protein level or ↓ albumin should prompt serum electrophoresis — patients with SS often have polyclonal gammopathy. Loss of a previously detected polyclonal gammopathosis can be observed in some patients with SS who develop lymphoma; development of a monoclonal gammopathosis can also signal the development of a lymphoma.
Hepatic alkaline phosphatase	Increased in primary biliary cirrhosis.
Liver transaminases	Elevated in chronic active hepatitis or hepatitis C. Mild increases in transaminases are observed in 5%-10% of patients with SS.
Serum bicarbonate	Low in distal renal tubular acidosis
Serum potassium	Hypokalemia in patients with SS with or without renal tubular acidosis
ESR	Often elevated, a nonspecific finding
SACE	Usually very elevated in sarcoidosis.
Immunology	
Investigation	Disease association
Rheumatoid factor	SS, rheumatoid arthritis, and SLE
ANAs	SS, and SLE
Antibodies to double-stranded DNA	SLE
Anti-Scl 70	Scleroderma
Antibodies to Ro and La antigens (extractable nuclear antigens)	SS—Anti-Ro antibodies found in 75% with primary SS and 15% with secondary SS Anti-La antibodies found in 40%-50% with primary SS and 15% with secondary SS
Antiphospholipid antibodies	Patients with SLE or primary SS may have positive test results for lupus anticoagulant antibodies
Cryoglobulins	Cryoglobulinemia in hepatitis C
Antimitochondrial antibodies	Primary biliary cirrhosis
Anti–smooth muscle antibodies	Chronic active hepatitis
Thyroid function	In some studies, patients with SS have increased frequency of autoimmune thyroid disease, with hypothyroidism in 10-15%.
Salivary gland imaging	
Technique	Features demonstrated
Sialography	Demonstrates ductal structure. Application for long-standing xerostomia. Demonstrates diffuse sialectasis. Useful for SS and salivary gland agenesis.
Salivary scintigraphy	Demonstrates site of functional salivary gland.
USS	Will demonstrate ductal and acinar structure. Useful for SS, HIV, and HCV-related salivary gland disease and malignancy.
CT	Demonstrates parenchymal structure. Useful for SS, HIV, and HCV-related salivary gland disease.
MRI	Demonstrates parenchymal structure. Useful for SS, HIV, and HCV-related salivary gland disease.
Gallium scans	Helpful in the diagnosis of sarcoidosis.
Histopathology of minor salivary gland tissue	
Disorder	Likely findings
SS	Focal aggregate of at least 50 lymphocytes and some plasma cells and macrophages. More than 1 focal aggregate per 4 mm^2. A score of >1 focus per 4 mm^2 has a specificity of 83.5%-95% and a sensitivity of 63%-81.8% in the diagnosis of SS. Predominantly $CD4^+$ T lymphocytes.
Sarcoidosis	Noncaseating granulomas
Lymphoma	Noninvasive lymphoplasmacytic infiltrate within which foci of follicle-center cells can be seen invading epithelial structures forming lymphoepithelial cells
HIV	Perivascular, periacinar, and periductal infiltrates of predominantly $CD8^+$ T lymphocytes. Multicystic lymphoepithelial lesions may also occur.
HCV	Lymphocytic infiltrate with a predominance of CD20 cells.
Hemochromatosis	Heavy deposition of iron in acinar and ductal epithelial cells and the absence of focal lymphoid cell infiltration.
Amyloidosis	Amyloid protein deposit that yields positive staining (eg, with alkaline Congo red)
Other investigational tools	
Investigation	Comment
Schirmer's test	Assessment of lacrimal gland function (positive when result is <5 mm). Useful in the diagnosis of SS, HIV, and HCV-related salivary gland disease and chronic sarcoidosis.
Rose bengal staining	Aniline dye that stains devitalized cells and is more sensitive than fluorescein staining. Conjunctival staining can be detected with the naked eye, and a slit-lamp examination enables the detection of abnormal uptake of stain in the cornea. A useful investigational tool for diagnosing possible SS.
Sialometry	Provides objective evidence of degree of decreased salivary flow, and thus helps confirm xerostomia, but the findings do not aid in the differential diagnosis.
Sialochemistry	Whole saliva from patients with SS may have elevated levels of sodium, chloride, lactoferrin, and immunoglobulin A, but these findings are not specific—thus, sialochemistry is not regarded as a useful investigational tool for diagnosing xerostomia.

Hb, Hemoglobin; *SS,* Sjögren's syndrome; *MCV,* mean corpuscular volume; *HIV,* human immunodeficiency virus; *SLE,* systemic lupus erythematosus; *ESR,* erythrocyte sedimentation rate; *SACE,* serum angiotensin-converting enzyme; *ANAs,* antinuclear antibodies; *HCV,* hepatitis C virus; *CT,* computed tomography; *USS,* ultrasound scan; *MRI,* magnetic resonance imaging.

Table VII. Summary of oral care in patients with xerostomia

Oral hygiene
   Plaque control, oral hygiene instruction, dietary advice, chlorhexidine mouthwash or fluoride mouthwash daily (0.05%) to minimize the risk of caries.
Dentures
   Should fit well. Implant-retained. Provide instructions on denture hygiene.
Antifungals
   Nystatin pastilles, amphotericin lozenges, miconazole gel
Topical saliva substitutes
   Sugar-free gum and candies; oral moisturizers
Systemic therapies
   Pilocarpine, cevimeline, and others

Table VIII. Some topical therapies for xerostomia

Sugar-free gum, candies, and liquids[96,97]
Lubricating gels, mouthwashes, lozenges, and toothpaste[99-103]
Salivary stimulant pastilles[104]
Mucin spray[105]
Humidifiers[107]
Saliva substitute placed in intraoral device[108]

Table IX. Systemic therapies for long-standing xerostomia

Therapy	Etiology
Likely to be of benefit	
Pilocarpine	Head and neck radiation
	SS
	Chronic graft-versus-host disease
	Drug-induced xerostomia
Bethanechol	Drug-induced xerostomia
Cevimeline	SS
Interferon α	SS
Carbacholine	Head and neck radiation?
Bromhexine	SS?
Corticosteroids	SS?
Hydroxychloroquine	SS?
Vitamin supplementation	SS
Acupuncture	SS
Electrostimulation	SS?
Evening primrose oil	SS?
Unlikely to be of benefit	
Azathioprine	SS
Cyclosporine	SS
Methotrexate	SS

SS, Sjögren's syndrome; ?, limited data.

cused on the development of systemic and sicca symptom questionnaires, and, in Europe, a prospective evaluation of systemic activity and damage measures is planned.

ORAL CARE OF LONG-STANDING XEROSTOMIA

Until recently, the management of long-standing xerostomia principally consisted of the avoidance of factors that might cause or aggravate dry mouth, the application of salivary substitutes, and the prevention of the associated oral complications.[94] However, local treatments have not always proved effective. The principal aspects of the management of long-standing xerostomia are summarized in Table VII. The different local and systemic methods for the management of xerostomia are discussed later.

Topical agents

Traditionally, treatment of dry mouth has focused on palliative measures with salivary substitutes, but because these are removed from the mouth during swallowing, the duration of their effect is short and they also lack the protective roles of saliva (Table VIII).[95] Saliva substitutes function in improving lubrication and hydration of oral tissues and maintaining oral health and function.

Sugar-free gum or sugar-free candies may help to increase salivary output, but they may be inconve-

nient and affect patients' compliance.[95] Frequent ingestion of sugar-free liquids may help.[93] A saliva substitute with a remineralizing effect on dentin and enamel and long-lasting relief of the oral symptoms of dry mouth is preferable.[97] Lubricating agents in the form of gels, mouthwashes, lozenges,[98] and toothpastes[99] have been used, with varying results, to relieve the symptoms of xerostomia.[100] The qualities of such lubricating agents that increase patients' acceptance and continued use of the agent include lubrication, taste, duration of action, the delivery system, severity of xerostomia, and cost.[101] Some available proprietary preparations include Luborant (Antigen, UK), Saliva Orthana (AS Pharma, Sweden), Salivace, and Oral Balance (Anglian, UK), which have been approved for dry mouth associated with radiation or SS.[102] Some are unsuitable for dentate patients because they cause the demineralization of teeth.

Salivary stimulant pastilles (Salivix, Provalis, UK) appear to be a useful adjuvant therapy for patients with dry mouth receiving oxybutynin chloride for detrusor instability, in that they allow higher doses of oxybutynin to be tolerated.[103]

In a recent study, a mucin spray was found to be useful against xerostomia in those who had undergone irradiation, with elderly patients deriving particular benefit from its use.[104] The results of one recent study of a topical oral moisturizer indicated significant subjective and objective improvements in

the signs and symptoms of xerostomia in individuals with SS and in those with head and neck cancer who had undergone irradiation.[105] Standard bedside humidifiers and hyperthermic, supersaturated humidification have been of minimal benefit.[106] An intraoral device containing saliva substitute and slowly releasing the lubricant into the mouth has proved more acceptable to patients with xerostomia than has the use of the lubricant alone.[107]

Systemic agents

Cholinergic agonists. Orally administered agonists of the muscarinic M3 receptor (pilocarpine and cevimeline) have been approved by the US Food and Drug Administration to increase salivary secretion (Table IX). The recent development of such muscarinic agonists serves an important step in recognizing the interaction between the immune and neuroendocrine systems.[108] The possibility of the use of cholinergic agents to stimulate salivation has always proved attractive. In the past decade, systemic pilocarpine has been found to be an effective means of managing xerostomia secondary to radiation of the head and neck; more recently, it has been discovered to have potential benefit in SS, especially where there is symptomatic extraoral exocrinopathy. Until the recent resurgence in interest in the possible efficacy of pilocarpine, there had been few detailed studies of the potential clinical benefits of cholinergics in the management of long-standing xerostomia. The use of pilocarpine and related agents to stimulate salivary flow may significantly improve the management strategy for SS.[109]

Pilocarpine. Pilocarpine is a parasympathetic agonist of acetylcholine muscarinic M3 receptors and thus stimulates secretion by exocrine glands such as the salivary, sweat, lacrimal, and respiratory mucous glands[110]; the contraction of smooth muscle; and the motility of the gastrointestinal and urinary tracts, gall bladder, biliary ducts, and bronchi.[111] These latter effects have dissuaded some clinicians to use pilocarpine.

Until the mid-1990s, the main clinical application of pilocarpine therefore centered upon its topical application in the management of glaucoma. Nevertheless, early reports suggested systemic pilocarpine to be of probable clinical use for the management of xerostomia associated with antihypertensive drugs[112] and tricyclic antidepressants,[113,114] but still there was little additional research until the early 1990s.[115]

Systemic pilocarpine has now been advocated for the management of the following:

1. Xerostomia secondary to radiation-induced salivary gland damage

2. Dry mouth of SS (approved in the United States and Europe).

In addition, systemic pilocarpine may be of potential benefit in limiting drug-induced xerostomia, but supportive data are awaited.

Pilocarpine is readily absorbed from the gastrointestinal tract, and peak plasma concentrations are reached within approximately 1 hour. Pilocarpine is metabolized by the liver and excreted principally by means of the kidneys, with the elimination half-life being approximately 1 hour.[116]

Systemic pilocarpine will increase exocrine gland secretion and may also give rise to adverse side effects that reflect its other cholinergic actions. Typical adverse effects are sweating, headache, nausea, mild abdominal pain and gastrointestinal upset, urinary frequency, chills and influenza-like symptoms, rhinitis, flushing, increased lacrimation, and palpitations. However, despite some of these being particularly frequent, they rarely restrict patient compliance or therapy.[117] Clinical experience to date suggests that pilocarpine is safe and well tolerated, with no serious adverse effects, tachyphylaxis, or drug-to-drug interactions of concern.[118] Nevertheless. systemic pilocarpine is probably best avoided for patients with respiratory disease (eg, asthma, chronic bronchitis, and chronic obstructive pulmonary disease) and those taking antihypertensive drugs because, although no notable drug interactions have been reported, interactions with β-blockers would seem possible.

Pilocarpine in the management of radiation-induced xerostomia. Brachytherapy of head and neck malignancies can cause profound xerostomia and salivary gland acinar destruction[24, 25, 119] when the radiation is directed through the major salivary glands. Thus, attempts are made to minimize the direct irradiation of the glands. One recent phase III randomized trial has suggested that amifostine administered intravenously before irradiation may lessen the severity of radiation-induced xerostomia.[120] In another recent study, a dramatic reduction of typical radiation-associated toxicities including xerostomia was observed in 25 patients when a 500-mg dose of amifostine was administered before radiochemotherapy (with an irradiation dose of 60 Gy and 2 cycles of carboplatin) of the head and neck region.[121] However, further trials are presently being conducted to confirm the efficacy of amifostine in reducing radiation-induced toxicities and to investigate its other possible applications.[122]

The results of open-label studies of orally administered pilocarpine in small numbers of patients after radiation suggested that it might lessen the severity of

radiation-associated xerostomia.[123-125] More recently, a number of double-blind and randomized, controlled trials have established that oral and perhaps high-dose topical pilocarpine may reduce the frequency and severity of radiation-induced xerostomia and associated symptoms.[126-131] More recently, 4 randomized, controlled trials were critically appraised, 3 of which used topical pilocarpine, and all reported subjective improvements in feelings of oral dryness, speaking, and chewing.[132] However, further evidence from other studies are needed before results can be generalized to the wider populations because the sample sizes in existing studies have varied and sampling methods were poorly defined.

The optimal dosage of pilocarpine is 5 mg 4 times daily or 10 mg 3 times daily; the pilocarpine is well tolerated generally. The pilocarpine should be prescribed for at least 8 to 12 weeks,[131] but long-term use of this agent would be expected in that full recovery of salivary gland function after radiation is unlikely.

Clinical benefit associated with oral pilocarpine may not always reflect salivary function before radiation or pilocarpine treatment.[131] Clinical response can vary between patients[110] and cannot be predicted with technetium 99m pertechnetate scintigraphy,[133] but it is estimated that the majority of patients likely to have clinical benefit with pilocarpine will be identified during the first 12 weeks of therapy.[134] The pilocarpine-induced enhanced salivary secretion may be possible for up to 7 months after radiation,[135] and it has been suggested that the administration of pilocarpine before[119] or during[136] the radiation may lessen the severity of any radiation-induced xerostomia.

Pilocarpine cannot increase the function of glands that are completely damaged by irradiation,[128] but it does appear to enhance the function of minor salivary glands that may be more resistant to the damaging effects of radiation compared with the major glands. Indeed, by virtue of their location in relationship to the direction of the brachytherapy, the minor mucous salivary glands of the palate and elsewhere may escape the full dose of radiation.[134-137] Provided residual functioning salivary tissue exists, pilocarpine administered in the form of an oral spray may be effective in relieving symptoms of dry mouth, but further investigation is warranted.[137] However, it has been suggested that because of its limited efficacy and its adverse effects, other local treatments should be tried before the institution of topical pilocarpine.[138] A more recent study concluded that no beneficial effect on radiation-induced xerostomia is found when pilocarpine is administered during radiation for head and neck cancer.[139]

Pilocarpine in the management of SS. The results of initial placebo-controlled studies of relatively small numbers of patients with SS suggested that systemic pilocarpine increased salivary flow within 2 to 3 hours of administration and reduced symptoms of xerostomia. This clinical benefit of orally administered pilocarpine has been confirmed in a large randomized, placebo-controlled, fixed-dose multicenter trial.[140-142] As in the aforementioned studies of radiation-associated xerostomia, a dosage of 5 mg of pilocarpine 4 times daily for at least 12 weeks is clinically beneficial. Unstimulated salivary flow significantly increases 1 hour after the administration of 5 mg of pilocarpine. In addition to increasing whole saliva flow, pilocarpine can increase labial minor salivary gland secretion,[143] perhaps suggesting that many patients with SS have at least some potential to benefit clinically from treatment with cholinergic agonists.

Pilocarpine therapy also reduced the frequency of oral and ocular symptoms related to xerostomia and xerophthalmia. These data suggest that pilocarpine may be of benefit in the symptomatic management of SS, but the studies have not included patients with absolute xerostomia, who may have the most severe oral symptoms of long-standing oral dryness.

Pilocarpine therapy may reduce the oral carriage of *Candida albicans* in SS,[144] but this is unlikely to be of notable significance to the oral signs or symptoms of long-standing dry mouth. Likewise, the precise influence of pilocarpine upon salivary IgA and cytokine secretion (if at all relevant to the disease process) remains unclear.[145]

Pilocarpine for xerostomia associated with cGVHD. Pilocarpine is likely to be of benefit in the management of xerostomia associated with cGVHD. The results of an open study suggested that orally administered pilocarpine reduced xerostomia-associated dysarthria and dysphagia in a small group of patients.[146-149] Oral pilocarpine (Salogen) 30 mg/day can alleviate cGVHD-induced xerostomia and improve the flow rate from the major salivary glands, resulting in the normalization of the altered salivary biochemical and immunologic composition in patients with cGVHD.[149]

Pilocarpine for drug-induced xerostomia. There have been few reports of the efficacy of pilocarpine in the management of drug-induced xerostomia. Early studies suggested that pilocarpine reduced the severity of xerostomia associated with antihypertensive and tricyclic antidepressant therapy,[112-115] but the results of a recent case report of antidepressant-associated oral dryness[150] and those of one animal study[151] suggest that pilocarpine is unlikely to be of benefit in the management of drug-induced xerostomia. However, the α_2 adrenoceptor antagonist yohimbine has been shown to have a sialogenic effect

on drug-induced dry mouth in a randomized, double-blind, crossover study.[152] However, the sample size in this study was very small.

Bethanechol. Bethanechol, which has both muscarinic and nicotinic agonist actions, was suggested to be of potential use in the management of drug-induced xerostomia.[153,154]

Bethanechol (25 mg, 3 times daily orally) was found to increase the unstimulated and stimulated salivary flow rates of patients with xerostomia secondary to radiation, but objective changes in salivary flow rates did not always correlate with symptomatic improvement.[155] However, adverse effects, which may include nausea and diarrhea, are infrequent.[153,155]

Cevimeline. Cevimeline ((±) cis-2-methylspiro [1,3-oxathiolane-5,3′-quinuclidine] mono-hydrochloride, hemihydrate; SNI-2011; Evoxac) is a quinuclidine analog of acetylcholine with a high affinity for M3 muscarinic receptors both of lacrimal and salivary glands but a low affinity for equivalent M2 receptors on cardiac and lung tissue.[156] Cevimeline increases lacrimal and salivary flow in normal rats and mice, in xerostomic mice with relevant autoimmune disease, and in rats with xerostomia secondary to irradiation.[157]

Double-blind studies suggest that cevimeline reduces the symptoms of xerostomia in patients with SS, yet the results of another study did not suggest that cevimeline was of benefit. It has been suggested that the required daily frequency of use of cevimeline (30 mg, 3 times daily) may be less than that for pilocarpine (ie, 5 mg, 4 times daily).[158] Therapy with cevimeline, 30 mg 3 times daily, seems to be well tolerated and provides substantive relief of xerostomia symptoms, whereas a dosage of 60 mg 3 times daily, although providing symptomatic relief, was associated with an increase in the occurrence of adverse events, particularly gastrointestinal tract disorders.[159] Treatment with cevimeline 30 mg 3 times daily increased salivary flow and improved the subjective and objective symptoms of patients with xerostomia associated with SS.[160,161] Cevimeline is metabolized principally in the liver and excreted through the kidneys and has a half-life of approximately 5 hours (far greater than that of pilocarpine; however, the adverse effects of cevimeline mirror those of pilocarpine).[158]

It has been suggested that cevimeline may have clinical application in the management of xerostomia secondary to irradiation, SS, HCV infection, and drug therapy,[160] but additional data are clearly required. It is another systemic treatment alternative in those with SS in whom topical saliva substitutes are of minimal or no benefit.[162]

Carbacholine. It has been suggested that carbacholine may be of benefit in the treatment of radiation-induced xerostomia,[125] but good published confirmatory data are lacking.

Anethole trithone. Anethole trithione has no cholinergic action, but it increases the availability of muscarinic receptors on the postsynaptic membrane and thus enhances the potential for cholinergic stimulation.[163-165] It has been shown to stimulate salivation and improve xerostomia.[166,167]

Anethole trithione may enhance pilocarpine-induced salivation in patients with radiation-induced xerostomia,[168] but it may not be of benefit in the management of primary SS.[169]

Pyridostigmine. Pyridostigmine is a cholinesterase inhibitor with both nicotinic and muscarinic agonistic action. Available data, including those from a placebo-controlled study, suggest that pyridostigmine may be of benefit in the treatment of drug-related xerostomia, but there are no data on the efficacy of this agent in the management of other common disorders giving rise to xerostomia.[110]

Bromhexine. Bromhexine (32-48 mg daily) may increase salivary and lacrimal flow in patients with SS[170,171]; however, there are few published data an the precise oral benefits of this therapy other than those of one study and the results of an animal study that suggested that bromhexine does not significantly alter the development or severity of SS-like disease.[172]

Other methods of stimulating salivation

Chewing gum. Chewing gum may enhance salivary flow routes, but these actions are likely to be transient and the wearers of full dentures may be unable to use them.[173] A combination of a mouthwash, toothpaste, and chewing gum in one study improved many of the symptoms of radiation-induced xerostomia,[174] and another study indicated that chewing gum may be more effective than artificial saliva in the management of xerostomia.[175] However, further randomized, controlled studies are needed to demonstrate the efficacy of chewing gum in the management of xerostomia.

Electrostimulation. It has been suggested that electrostimulation may increase salivary flow in some patients with SS,[176] and one study has shown an improvement in xerostomia symptoms in a group of persons with SS who were treated with electrostimulation.[177] Nonetheless, further trials are needed to support such claims.

Acupuncture. The results of studies of patients with radiation-induced xerostomia, but not SS,[178-182] have suggested that acupuncture may cause a sustainable increase in the salivary flow rates of those with SS. One report has suggested that acupuncture may provide

some symptomatic improvement in some patients requiring palliative care,[183] and another more-recent study demonstrated the benefits of a regimen of 3 to 4 weekly treatments followed by monthly sessions.[184]

Dietary supplementation. The results of 1 placebo-controlled investigation suggested that a herbally based agent with vitamin supplements (LongoVital, LV, Denmark) cause a prolonged increase in unstimulated salivary flow and a reduction in rose bengal dye scores in a group of patients with SS.[185]

It has been suggested that evening primrose oil, rich in fatty acids and important in inhibiting 2-series prostaglandins, may enhance salivary flow in some individuals with SS.[186-188] It has also been suggested that those with drug-induced xerostomia may benefit from chewing cappuccino coffee, yet only temporary improvement is provided for xerostomia.[189] Positive effects on symptoms in patients with SS were seen after the use of linseed extract Salinum with or without chlorhexidine.[190]

Immunologically active agents

SS is an autoimmune exocrinopathy characterized by a destructive T-lymphocyte response and the release of a range of cytokines.[94] Thus, if it were possible to modulate these responses, it might be possible to suppress gland damage. A number of modalities have been explored.

Interferon α. The results of open-label studies have suggested that intramuscular (eg, 1×10^6 IU/wk[191]) and parenteral (3×10^6 three times weekly[192]) interferon α increases the lacrimal and salivary flow of patients with primary and secondary SS. However, in contrast, systemic interferon α commonly gives rise to a wide range of adverse effects including xerostomia[193] and perhaps SS[194]; thus, lower dosage modalities were indicated. Subsequent open-label and single-blinded studies also suggested that interferon α–containing lozenges (150 IU interferon α 3 times daily) might reduce the severity of xerostomia in primary and secondary SS, with clinical benefit being observed in some persons after 9 weeks of therapy.[195-197] Both the parenteral and oral interferon α therapy caused a reduction in the mononuclear cell infiltrate and increased the normal architecture of examined labial salivary glands. A randomized, controlled study confirmed that therapy with interferon α lozenges (150 IU 3 times daily) for 12 weeks tended to increase unstimulated salivary flow, significantly increased stimulated whole salivary flow, lessened associated oral symptoms, and did not give rise to adverse side-effects. A higher dosage of interferon than 150 IU does not impart any additional benefit.[198]

The precise mechanisms by which oral interferon α increases salivary function in SS remain unclear because interferon is inactivated by the gastrointestinal tract and is not detectable in blood after oral ingestion. However, interferon α augments the transcription and production of aquaporin-5, which, in vitro, is a membrane-bound protein important in lacrimal and salivary gland function[199]; therefore, interferon α may act by both attenuating autoimmune-driven salivary gland damage and influencing water transportation through the up-regulation of aquaporin-5.

Corticosteroids. Systemic corticosteroids may be beneficial for the management of accompanying connective tissue disorders, but there are conflicting data of the precise benefits in reducing the oral or ocular symptoms of SS. The results of one randomized study suggested that prednisolone (30 mg on alternate days) was effective,[200] whereas a more recent investigation found that lower doses of prednisolone were not clinically useful (although the levels of relevant serologic markers did fall).[201] Of interest, corticosteroid irrigation of the major glands (eg, with prednisolone 2 mg/mL in saline solution) may be clinically useful by increasing salivary flow rates, particularly in patients in the early stages of disease.[202] A recent case study reported that oral prednisolone improved acetylcholine-induced sweating in a patient with anhidrosis related to SS.[203] Another case study reported an improvement in clinical, histologic, and immunohistologic parameters after the use of high-dose steroids in the treatment of SS.[204]

Hydroxychloroquine. Hydroxychloroquine may be of some clinical benefit at dosages of 6 to 7 mg/kg/day, producing a reduction in serum IgG and IgM levels and C-reactive protein and erythrocyte sedimentation rates and a fall in salivary levels of IL-6 in SS,[205-208] all without causing significant retinopathy.[205,206] However, the clinical efficacy of hydroxychloroquine appears variable and benefit may only occur if the drug is prescribed for periods greater than 1 year.[205,208-212] Long-term studies are therefore required to determine the precise clinical benefits of hydroxychloroquine in the management of SS.[213,214]

Other Immunosuppressants

Azathioprine has not proved effective for the management of the xerostomia of SS [215]. Systemic cyclosporine produced some improvement in subjective xerostomia, but it did not produce any other relevant clinical improvement.[216]

Cyclophosphamide was reported to be of benefit in the management of secondary SS in one young adult [217]. Sulfasalazine was not of benefit in the treatment of primary SS.[218] Methotrexate does not seem to

be of significant clinical use in the management of SS.[219] Thalidomide may be of potential benefit in the management of immunologically mediated salivary gland disease (eg, SS, sarcoidosis, and HIV and HCV disease), probably by virtue of its anti–tumor necrosis factor α activity,[220,221] but relevant detailed clinical evaluation of this agent is required.

Other inhibitors of chemokine function or receptors may ultimately prove to be helpful in the management of SS, but at present the benefits of these and inhibitors of de novo pyrimidine synthesis for the management of long-standing immunologically mediated xerostomia[222] remain unknown.

Other Systemic Therapies

An association between SS and retroviral infection seems unlikely,[223] but one open-label study suggested that zidovudine increased salivary flow and lessened the symptoms of xerostomia in a group of patients with SS but not HIV disease.[224] Highly active antiretroviral therapy may reduce the salivary gland enlargement of HIV-related salivary gland disease.[225] A recent study has suggested that an hydrous crystalline maltose may cause adjective and symptomatic improvement in both xerostomia and xerophthalmia,[226] whereas ambroxol (Mucosolvan) 135 mg daily for 8 weeks was shown in another study to improve sicca symptoms in those with SS.[227] Sustained improvement of active primary SS may be possible with infliximab treatment. One recent study demonstrated a statistically significant decrease in global and local disease manifestations in 10 patients after regular infusions of infliximab for 1 year.[228]

CONCLUSION

As new infections emerge (eg, HIV and HCV), patient lifespan increases, and new drug therapies continue to be developed, it is likely that more individuals will have the symptoms and signs of long-standing xerostomia. The treatment of xerostomia has improved as a consequence of the wider ranges of available topical or systemic therapies. A wide range of systemic therapies have been advocated for the management of long-standing xerostomia—many would seem to be ineffective. At present, the anticholinergic agents would seem to hold promise and are appropriate for the treatment of xerostomia associated with radiation and SS.

However, there is a need for well-controlled and appropriately designed clinical trials of therapies for the treatment of xerostomia. Few of the available agents have been extensively tested. At present, the immunologically mediated salivary gland disease of SS is poorly understood and does not seem to respond to immunosuppressive therapy.

Future treatments for some of the salivary gland disorders may require the use of gene therapy and tissue engineering,[229] but at present there is a need to have a greater understanding of the causes and pathogenesis of salivary gland disease before specific therapies can be developed.

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