

Stomatological approach to Sjögren's syndrome: diagnosis, management and therapeutical timing

F. MINOZZI, M. GALLI, L. GALLOTTINI, M. MINOZZI*, V. UNFER

I Faculty of Medicine and Surgery, Department of Odontostomatological Sciences; and

*Department of Obstetrics and Gynecology, University of Rome "La Sapienza", Rome (Italy)

Abstract. – Sjögren's syndrome is a chronic multisystem autoimmune disease characterized by the exocrine glands inflammation, with subsequent hypofunction. More frequently lachrymal and salivary glands are interested with subsequent xerophthalmia and xerostomia. Sjögren's syndrome can be present in an idiopathic type or in association with other autoimmune diseases as rheumatoid arthritis, systemic lupus erythematosus, sclerodermia, etc. It interests mainly the women (with a ratio F:M=9:1) with an age between 40 and 60 years old. The disease prevalence varies from 0.4% to 4.8%. The glandular lesions determine in the time a volume reduction and a secretum quality alteration. The most frequent oral manifestations are xerostomia, that allows the establishment of caries, gingivitis, periodontal disease and oral candidiasis.

The aim of this work was to perform a thorough review of the literature on Sjögren's syndrome, illustrating the most internationally accredited diagnostic criteria, the patient's management and therapeutical approach in the odontostomatological discipline.

The Authors conclude that it doesn't exist a resolute treatment of the disease. The therapy is only palliative, and is turned to the treatment of xerostomia and xerophthalmia, through systemic and aspecific sialogogues drugs. From the odontostomatological point of view, particularly useful results the domiciliary and professional oral hygiene to contrast the xerostomia effect on the oral structures.

Key Words:

Sjögren's syndrome, Odontostomatological approach, Salivary glands, Lachrymal glands, Differential diagnoses, Management, Odontostomatological treatment.

Introduction

Sjögren's syndrome is a systemic autoimmune disease with an inflammatory characteristic, that

from the nosographic point of view can be present in an isolated type (idiopathic or primary), or in a secondary type, in association with other autoimmune diseases as rheumatoid arthritis, systemic lupus erythematosus or sclerodermia. In both the cases, the disease peculiar characteristic is the exocrine glands anatomical and functional involvement that is translated in the classic "sicca syndrome" which hinges are represented by xerostomia and xerophthalmia. Beyond the exocrine glands involvement, Sjögren's syndrome can potentially interest any organ and apparatus with extremely pleiomorphic clinical manifestations even if in literature the extraglandular complications frequency is heterogenous, in part also for the different classification criteria set used in the selection of patients. Generally, there is the common conviction that the extraglandular manifestations of the Sjögren's syndrome are tendentially of modest intensity and relatively stable in the time while the more frightening complication for the patients prognosis is the possible lymphoproliferative onset with a relative risk of lymphoma, estimated around to 6.4 cases for 1000/year. Follow-up longitudinal studies on wide patients casuistries are relatively insufficient and, sometimes badly comparable, not only for the different classification criteria employed but also for the contemporary inclusion of patients with primary and secondary Sjögren's syndrome and for the study design, often, focused on a single organ or apparatus engagement analysis.

The aim of the present work was to describe the main aetiopathogenetic, clinical and anatomopathological characteristics of the syndrome, and to illustrate the most internationally accredited diagnostic criteria, the patient's management and therapeutical approach in the odontostomatological discipline.

Sjögren's Syndrome Definition, Historical Background and Epidemiology

Sjögren's syndrome is an inflammatory chronic immune-mediated disease characterized by lymphocytes infiltration and lachrymal and salivary glands acini destruction² (autoimmune exocrinopathy). The main target is the salivary and lachrymal glands tubular epithelium, giving the characteristic symptoms of ocular and oral dryness³.

The lachrymal and salivary functions can be modified by many factors over the inflammation, as drugs consumption, infections, irradiations and by the autonomous nervous system (ANS). In making a diagnosis the specialist must take in consideration the disorders that can simulate Sjögren's syndrome, as glandular age-related atrophy, chronic anxiety, and a spectrum of functional disorders in the chronic fatigue syndrome/fibromyalgia group, in which there are dry eyes and mouth symptoms⁴.

Sjögren's syndrome is distinguished in two forms²:

- Primary Sjögren's syndrome – association between mouth dryness (xerostomia) and ocular dryness (xerophthalmia or keratoconjunctivitis sicca);
- Secondary Sjögren's syndrome – association between xerostomia, xerophthalmia and connective tissue disorder (usually rheumatoid arthritis) or other associated autoimmune diseases such as systemic lupus erythematosus (SLE), sclerodermia, primary biliary cirrhosis, mixed connectivitis and pernicious anemia (Biermer's disease)⁵.

The most common symptoms in the two forms of Sjögren's syndrome are the extreme fatigue

and that related to xerophthalmia, xerostomia, and arthritic manifestations.

Generally, the ocular and oral manifestations are more grave in the primary Sjögren's syndrome that is the type mainly predisposed to malignant lymphoma transformation².

The exocrinopathy involves frequently the skin secretory glands, the respiratory tract and the urogenital tract. About one-third of patients have also extraglandular manifestations mediated by immune complexes and vasculitis, clinical features as arthritis, interstitial pneumonia, nephritises, neuropathies and central nervous system (CNS) involvement³.

The clinical manifestations of Sjögren's syndrome can be various, reason for which the patient's management is turned to the specific resolution of every case.

Sjögren's syndrome is a relatively recent disease (Table I).

Sjögren's syndrome interests mainly feminine sex individuals with an age between 40 and 60 years old (with a ratio F:M=9:1) (in the primary type it interests the 0.3-1.5% of the population with a prevalence of 3% in the geriatric population).

The beginning symptoms are frequently referred to the mouth and eyes dryness and irritation. Xerostomia can be associated with difficulty in the swallowing and in the conclusion of the phonetic function, increase of liquids consumption and taste alterations^{2,6,7}.

It predisposes also to the oral candidiasis^{5,8,9} that interests approximately 70% of the patients and justifies the mucosa irritation and reddening, it predisposes to bacterial sialadenitis and to rapidly progressive caries. The oral mucosa appears dry, smooth, and shiny. The tongue alterations can be important. The tongue dorsal side

Table I. Chronology of Sjögren's syndrome descriptions⁴.

1888	Single case reports by Hadden and Rowlands
1892	Case report and histology described by Miculicz
1926	Three patients described by Gougerot
1928	Link with arthritis reported by Houwer
1933	Sjögren's thesis describing 19 patients with "keratoconjunctivitis sicca"
1946	Sjögren's thesis translated into English
1953	The term "Sjögren's syndrome" becomes established in literature
1965	Primary versus secondary Sjögren's syndrome described
1970	Autoantibodies Ro (SS-A) e La (SS-B) described. Routine diagnostic tests available in 1990's.
1980 and 1990	Extraglandular manifestations
1990	Trials of disease-modifying drugs
1993	The preliminary European criteria
2002	The revised American-European consensus criteria

often appears reddish and atrophic and shows various degrees of cracks and lobes. The keratoconjunctivitis sicca is manifested with ocular dryness that provokes a burning sensation and a foreign body sensation².

The salivary glands volume increasing results referred approximately by the 30% of the patients², while is clinically manifested only in the half of this cases. It interests mainly the parotid glands, often bilaterally, and rarely it presents allergic symptomatology.

Aetiology and Pathogenesis

The aetiology and the pathogenesis of Sjögren's syndrome are not clear although immunological and histopathological dates support for an autoimmune pathogenesis, characterized by hyperreactivity of the lymphocytes B and by the production of various antibodies. The rheumatoid factor, associated with many other autoimmune diseases, is present in the greater part of patients with primary or secondary Sjögren's syndrome, as they are present various antinuclear antibody factors. These include autoantibodies directed on the nuclear antigens known as Ro and La, named also SS-A and SS-B^{10,11}, respectively.

The precipitate anti-Ro antibodies are found in approximately 75% of the patients with primary Sjögren's syndrome. The anti-La antibodies can be found in the 40% of the patients with Sjögren's syndrome. These antibodies are not specific of the disease, but they are useful under the diagnostic profile, because they can be individuated in a period that precedes the appearance of the concomitant clinical feature². In the 50% of patients are present antibodies directed on the salivary ducts, but they not seem to be related on the disease gravity.

Some Authors¹², considering the fact that Ro and La are expressed on the surface of apoptotic cells and that the apoptosis in salivary epithelium is increased in Sjögren's syndrome, consider that it is possible that an immune response to these antigens in apoptotic tubular cells could contribute to the inflammation in the gland.

Recently, have been reported two Sjögren's syndrome autoantigens, fodrin protein, involved in apoptosis and the muscarinic acetylcholine receptor M3¹³⁻¹⁵. The anti-M3 antibody is particularly interesting because it acts as a potential antigen and it is involved in the pathogenesis as it could cause an exocrine dysfunction by block-

ing the neurotransmission. The antibody was originally described as an indirect effect of IgG on inhibiting M3 function on whole organs in *ex vivo* systems. Actually, the anti-M3 antibodies have not been demonstrated in the immunological tests, and their existence remains in question.

Naturally, it is possible that the inhibiting antibodies do not react with M3 itself but with an associated protein that affects its function. It was suggested also a viral hypothesis with the possible aetiological role of the cytomegalovirus (CMV), of Epstein-Barr virus (EBV), of the human herpesvirus of type 6 (HHV-6).

The presence of Epstein-Barr virus DNA has been detected in salivary and lachrymal glands, although the data evidence that the virus acts simply using the glands as a site of persistence rather than causing the inflammation in Sjögren's syndrome. However, Epstein-Barr virus is still considered to be a candidate for involvement in the pathogenesis of this syndrome.

Retroviruses have been implicated in Sjögren's syndrome as they are known to infect cells of the immune system and can cause abnormalities of immune regulation. A subgroup of patients with human immunodeficiency virus infection develop diffuse infiltrative lymphocytosis of the salivary glands and other organs with CD8 + T-cells mainly. The clinical presentation can be very similar to that of Sjögren's syndrome⁴. Recent large-scale studies have suggested that patients with diffuse infiltrative lymphocytosis comprise between 3 and 8% of human immunodeficiency virus infections¹⁶. A similar syndrome has also been described in association with the other major human retroviral pathogen, human T-leukaemia retrovirus-I (HTLV-I).

Although rare in the UK, HTLV-I is thought to underline the condition in up to 20% of patients presenting with Sjögren's syndrome in endemic areas such as Japan. Conversely, *sicca* symptoms are found in about 3% of patients infected with HTLV-I.

Given that diseases resembling Sjögren's syndrome occur in a proportion of infections with the two known major retroviruses in humans, the research has been on far new retroviruses in idiopathic disease. The earliest positive finding was the demonstration of retroviral A-type particles in lymphoblastoid cells co-cultured with homogenates of salivary glands from patients with Sjögren's syndrome¹⁷. It was defined a new retroviral sequence from a patient with Sjögren's syndrome, although were not possible to link it to the disease¹⁸.

Green et al. described, on the base of experiments on a HTLV-I tax transgenic mouse¹⁹, that it was visible the development of a sialadenitis characterized by a focal proliferation of ductal epithelial cells within the major and minor salivary glands, followed by lymphocytic infiltration. This experiment is of interest because it demonstrates how a single viral gene product can generate inflammation²⁰ and explores how HTLV-I (and potentially other viruses) can cause the chronic inflammation of Sjögren's syndrome. There are several studies that provide to search the involvement of retroviruses in Sjögren's syndrome, although careful and systematic searches for a single agent have yet to be successful.

There are also genetic factors that predispose to that disease. Primary Sjögren's syndrome is strongly associated with the HLA-DR3 gene, B8-related genes and DQ2 and C4A gene²¹.

Approximately 5% of the patients affected by Sjögren's syndrome can develop a lymphoma. This presents progressive, diffuse or nodular enlargement of the salivary glands, lymphadenopathy or pulmonary nodules. The patients affected by Sjögren's syndrome with a chronic B-cell stimulation, can develop a 44-fold increased risk of malignant change in the interested structures as developing non-Hodgkin's lymphoma²².

The prognostic indicators of a lymphomatous evolution are:

- the reduction of the immunoglobulins plasmatic levels (mainly IgM);
- the reduction of the rheumatoid factor title;
- the increasing of β 2-microglobulin;
- the presence of a monoclonal population in the glandular infiltrate.

Histopathological Aspects

The histological aspect presents a diffuse periductal lymphocyte infiltration (mainly lymphocytes, histiocytes and few plasmacells) that sometimes dissociate the glandular structures. Often germinative centers are present. In some cases the infiltration is so intense that it simulates a lymphomatous feature. The conglomate lesion is typically constituted by lymphoid cell expanses that encircle epimyoepithelial islands and substitute completely the salivary gland lobules (myoepithelial sialadenitis).

It has been demonstrated that lymphocyte migration is mediated by VCAM-1 (*vascular cell*

adhesion molecule) and PNA_d (*peripheral node addressin*) expressed on vascular endothelium. Inhibition of these two molecules or their ligands (α 4-integrin, I-selectin and lymphocyte function-associated antigen-1, LFA) showed a nearly complete block of lymphocyte migration into the lachrymal glands of non autoimmune mice.

Epithelial cells seem to be activated in Sjögren's syndrome. They produce several pro-inflammatory cytokines (IL-1, IL-6, TNF- α), indicating that epithelial cells may act as "non-professional" antigen-presenting cells (APC). The production of chemokines (CXCL13, CXCL12, CCL21 ECL, PARC) by epithelial cells could contribute to ectopic germinal center-like structure formation. Epithelial cells express some molecules (Fas, FasL and Bax) suggesting increased apoptosis as a major mechanism responsible for acinar cell destruction. The increased matrix metalloproteinase activity (MMP-2, MMP-3, MMP-9) could be related to the dramatic changes in the structural organization in the basal lamina and apical surface of acini²³.

Diagnosis

Sjögren's syndrome diagnosis must be formulated in an interdisciplinary within through the collaboration of four professional figures, as the dentist, the oculist, the rheumatologist and the histopathologist. It rests on the presence of a clinical, serological, instrumental and histopathological parameters series. However they are classification criteria that in the clinical practice must be used with secure because they are not diagnostic or equipped with high specificity but with relatively low sensibility. It was proposed so a diagnostic algorithm (Figure 1), a decisional tree that can result particularly useful in the initial disease phases when the clinical table is still not totally expressed.

The classification criteria most accredited in the international scientific literature, on which is based the Sjögren's syndrome diagnosis are that of Vitali et al.²⁴⁻²⁷ (Tables II and III)

The first criterium evaluates the ocular symptoms through the positive answer to at least one of the three questions asked to the patient, as indicated in the Table II, Criterium I.

The second criterium evaluates the oral symptoms through the positive answer to at least one of the three questions asked to the patient, as indicated in the Table II, Criterium II.

Figure 1. Sjögren's syndrome (SS) decisional tree.

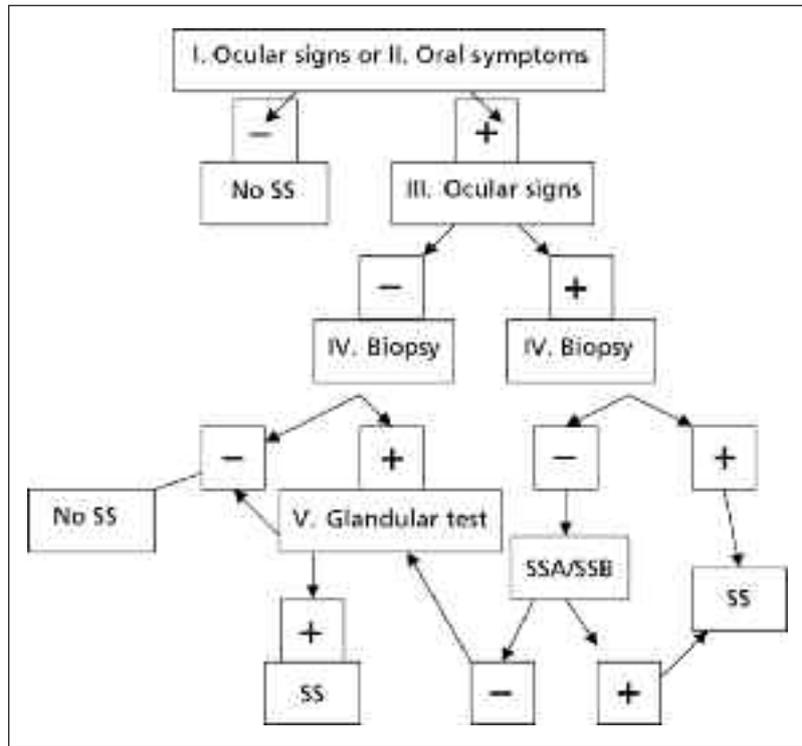


Table II. Classification criteria for Sjögren's syndrome diagnosis²⁰.

<p>Ocular symptoms: a positive response to at least one of the following questions:</p> <ol style="list-style-type: none"> 1. Have you had daily, persistent, troublesome dry eyes for more than 3 months? 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? <p>Oral symptoms: a positive response to at least one of the following questions:</p> <ol style="list-style-type: none"> 1. Have you had a daily feeling of dry mouth for more than 3 months? 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? <p>Ocular signs (- ie, Objective evidence of ocular involvement defined as a positive result for at least 1 of the 2 following two tests):</p> <ol style="list-style-type: none"> 1. Schirmer'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) <p>Histopathology:</p> <p>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 adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm² of glandular tissue</p> <p>Salivary gland involvement-Objective evidence of salivary gland involvement defined by a positive result for at least 1 of the following diagnostic tests:</p> <ol style="list-style-type: none"> 1. Unstimulated whole salivary flow (<1.5 ml in 15 min)* 2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitory 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 <p>Autoantibodies-Presence of 1 or both of the following autoantibodies in the sera:</p> <ol style="list-style-type: none"> 1. Antibodies to Ro (SSA) antigens; 2. Antibodies to La (SSB) antigens

*This test must not be kept in consideration in the subjects over 60 years old, where the reduction can be related to the age.

Table III. Classification criteria for Sjögren's syndrome diagnosis²⁰.

<p>The classification rules are:</p> <p><i>For primary Sjögren's syndrome</i> In patients without any potentially associated disease, primary Sjögren's syndrome may be defined as follows:</p> <ol style="list-style-type: none"> 1. The presence of any 4 of the 6 above mentioned items is indicative of primary Sjögren's syndrome, as long as either item IV or VI yields positive results. 2. The presence of any 3 of the 4 following objective criteria: III, IV, V or VI. 3. The classification procedure represents a valid alternative method for classification, although it should be more properly used in a clinical-epidemiologic survey. <p><i>For secondary Sjögren's syndrome</i> 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 Sjögren's syndrome.</p> <p><i>Exclusive criteria</i> Past head and neck radiation treatment; Hepatitis C infection; Acquired immunodeficiency syndrome (AIDS); Pre-existing lymphoma; Sarcoidosis; Graft-versus-host-disease; Use of anticholinergic drugs</p>

Through the third criterium the ocular signs are evaluated, that is the ocular involvement objective evidence defined by the positivity to at least one of the two tests (Schirmer's test and Rose Bengal test):

Schirmer's test consists in the positioning of thin strips of absorbent paper between the eyeball and the most lateral part of the inferior lid, to contact with the inferior lachrymal gland, for the tear flow evaluation. The test is positive if the strips are bathed for a distance of 5 millimeters or less, in a time of 5 minutes. It is important to execute the test without anesthesia, to not alter the result.

Rose Bengal is a vital stain that colors the cells that have lost the glycoproteic protection; it colors moreover the mucus. The Rose Bengal staining test consists in introducing a Rose Bengal drop in the conjunctival area and performing the staining degree evaluation (according to Van Bijsterfeld^{28,29}) dividing the ocular surface in three zones: the nasal conjunctive, the temporal conjunctive and the corneal surface. For each zone a score from 0 to 3 is considered, for a maximum total of 9 for each eye examined. A score ≥ 4 indicates the test positivity.

Is useful to perform for the diagnosis also the "Break Up Time-B.U.T." test that evaluates the breaking time of the lachrymal film. This last is performed introducing a fluorescein drop in the conjunctival area and observing, to the blue cobalt light of the fissure lamp, the time that

elapses between the last winking and the formation of dark areas on the corneal surface. A breaking time of the lachrymal film inferior to 10 seconds is considered pathological, because it indicates anomalies in the mucine and in the lipidic layer.

The staining with Lissamine Green vital stain (Lissamine Green test) is an optimal alternative to Rose Bengal stain. It is few less selective, mainly with the mucus, but it is better tolerated by the patient (that it does not feel absolutely nothing). The relationship with the suffering of the mucipar cells is optimal. It allows to evaluate the ocular surface characteristics and the tear film integrity.

The fourth criterium is the main diagnostic surveying to formulate the Sjögren's syndrome diagnosis.

It consists in the minor salivary glands biopsy and successive histopathological analysis. The histopathological characteristic of the minor salivary glands is that of a lymphocytic sialadenitis. It consists in the presence of focal aggregates of at least 50 lymphocytes, plasmacells and macrophages adjacent to the acins and replacing the glandular parenchyma. This foci are present in all or nearly all the glandular tissue in examination. More larger foci often show the presence of germinal centers while the epi-mio-epithelioid islands, typical of the benign lympho-epithelial lesion of the major salivary glands are rare. The focus score (number of foci for 4 square mm)

must be ≥ 1 , according to Chisholm e Mason³⁰ classification criteria (Table IV).

The fifth criterium evaluates the salivary glands involvement, defined by the positivity of at least one of the three diagnostic tests:

- Sialometry, that evaluates the stimulated and unstimulated salivary flow. The test is insufficiently specific. Values of the unstimulated salivary flow inferior to 1.5 ml in 15 minutes indicate the test positivity. This test must not be held in consideration in the subjects over 60 years old, where the reduction can be related to the age.
- Sialography and Sialo-NMR: is a radiographic survey that allows to analyze the presence and the degree or stenosis of the ductal system. It has the sensibility and the specificity comparable to the histological examination of the minor salivary glands. The sialo-NMR is a less invasive technique comparable for the specificity and the sensibility both to the traditional sialography and to the labial biopsy. The test positivity is given by the presence of diffuse sialectasies in the parotid sialography without main ducts obstruction evidence.
- Scintigraphy: it estimates the ^{99m}Tc-pertecenate uptake speed and density of all the salivary glands. The salivary scintigraphy that shows delayed uptake, reduced concentration and/or delayed radioactive isotope excretion, indicates the test positivity.

The sixth criterium evaluates the presence in the serum of at least one of the following specificities: the autoantibodies Anti-Ro (SSA) and Anti-La (SSB), the presence of antinuclear antibodies (ANA), and the rheumatoid factor.

Table IV. Chisholm and Mason classification criteria.

Degree 0:	Normality, absence of any infiltrate
Degree 1:	Modest infiltrates, limited to few cells scattered
Degree 2:	Moderate infiltrates, with cellular groupings that however do not reach the focus entity
Degree 3:	Only one focus of infiltrative cells
Degree 4:	Two or more foci of infiltrative cells

The entity of the infiltrates is reported to a conventional surface of 4 square mm, correspondent to a microscopic field of 2 millimeters of diameter. It is to consider significant for the diagnosis the medical report of two or more foci of infiltration for a square mm

The norms for the diagnosis of primary and secondary Sjögren's syndrome in the light of the six classification criteria, and the exclusion diagnostic criteria are indicated in the Table III.

Laboratory Exams

The more common haematological exams alterations are represented by the erythrocyte sedimentation rate (ESR) increase, the plasmatic concentrations increase of different immunoglobulin IgG classes, moderate anemia, leucopenia and eosinophilia.

There are present also various antibodies:

- in the 75% of the cases there is a positivity on the rheumatoid factor, also in the absence of joint lesions;
- antinuclear antibodies;
- precipitate antinuclear antibodies as SS-A and SS-B.

The SS-A and SS-B antibodies are present both in primary and secondary Sjögren's syndrome. It is useful to underline that these autoantibodies are not specific: the demonstration of their presence has not a diagnostic mean if it is separated from other clinical elements.

Studies of immunological typization demonstrated the expression of some histocompatibility antigens in the patients with primary or secondary Sjögren's syndrome. The presence of HLA-DR4 antigen was demonstrated in the patients with secondary Sjögren's syndrome. The histocompatibility antigen more frequently associated to the primary Sjögren's syndrome is HLA-B8.

Extraglandular Manifestations

As other systemic autoimmune diseases also Sjögren's syndrome can be present with a symptomatologic complex constituted by constitutional symptoms, as asthenia, malaise and arthralgia-arthritis, sometimes associated to modest fever. However, in the Sjögren's syndrome are characteristic the xerophthalmia, the xerostomia and the xerotrachea. In the case of a secondary type will be present also typical symptoms of the main disease.

The more frequent extraglandular manifestations (Table V) are the muscle-skeletal apparatus involvement (arthralgias cases that interest the small articulations of the hands and the wrists, not erosive arthritis), of the urogenital apparatus

Table V. Manifestations of Sjögren's syndrome².

Glandular (Exocrine glands)	
<ul style="list-style-type: none"> • Salivary • Lachrymal • Cutaneous • Respiratory tract • Pharynx and gastrointestinal tract • Reproductive system 	<ul style="list-style-type: none"> • Xerostomia • Xerophthalmia • Xerodermia • Nasal dryness, sinusitis, tracheitis • Disphagia, atrophic gastritis, pancreatitis • Vaginal dryness
Extraglandular	
<ul style="list-style-type: none"> • Articular manifestations • Cutaneous • Hepatic • Renal • Endocrine • Neurological • Hematological • Immunological 	<ul style="list-style-type: none"> • Arthritis • Purpura, Raynaud's phenomenon • Primary biliary cirrhosis • Renal tubular disorders • Thyroiditis • Central and perypheral neuropathies • Anemia, Leucopenia, Thrombocytopenia • Autoantibodies, Hypergammaglobulinaemia

(vaginal dryness, dyspareunia, recurrent infections of the urinary ways) and haemopoietic (leukopenia, anemia, deficiency of platelets).

Pulmonary pathologic findings have been described in 10-30% of the cases, but with a very variable incidence in the different casuistries, also on the base of the adopted technique. The torax radiography is pathological in about 10-30%, High Resolution Computed Tomography (HRCT) in 35-50% of the cases. The evolutive interstitial fibrosis (UIP), with classical honeycombing, has been reported in more than 10%, more frequently in the case of secondary Sjögren or primary disease, associated with extraglandular lesions.

The airway disease is very common in Sjögren's syndrome and it comprises consolidation areas (bronchiolitis obliterans organizing pneumonia: BOOP), centrilobular nodules with peribronchial thickening (follicular bronchiolitis), geographical air-trapping (constrictive bronchiolitis) and bronchiectasis.

Other pathological aspects are represented by areas of atelectasis, pleuritis, pulmonary arterial hypertension (plexogenic vasculopathy).

The pulmonary lymphoma BALT (Bronchial Associated Lymphoid Tissue) complicates Sjögren's syndrome in about 25% of the cases and it is expressed radiologically with chronic consolidative areas, associated to the air bronchogram.

Less common (5%) is non-Hodgkin B cell lymphoma, causing adenopathies, nodules or pulmonary masses; rarely the pulmonary lesions are isolated.

The incidence of the Sjögren's syndrome manifestations is mentioned in the Table VI.

Ocular Manifestations

The lachrymal glands involvement determines a volume reduction and a lachrymal quality alteration. The reduced watery component of the precorneal film causes the subjective feeling of dry eye, while, at the same time, the mucous component is accumulated as thin filaments that attacked themselves closely to the corneal epithelium³¹.

When the right viscosity of the tear film is a lot altered the palpebral movements can determine conjunctive and corneal superficial epithelium lesions until the classical findings of

Table VI. Incidence of Sjögren's syndrome manifestations.

<p>Xerophthalmia: 47%</p> <p>Xerostomia: 42%</p> <p>Arthritis: 20%³</p> <p>Parotid swelling: 60%³</p> <p>They are divided in:</p> <ol style="list-style-type: none"> 1. Parotid swelling due to diseases 2. Parotid swelling due to infections 3. Parotid swelling due to lymphoma <p>Fatigue: 70% of the patients with primary Sjögren's syndrome³</p> <p>Raynaud's phenomenon: 30%³</p> <p>Pulmonary diseases: 25%³</p> <p>Rheumatic polymyalgia: 3%³</p> <p>Neurological involvements: 1%³</p> <p>Clinically relevant renal diseases: 5%³</p> <p>Diminished vaginal secretions: 30%⁴</p> <p>Sjögren's lymphoma: 5%⁴</p> <p>Dyspareunia: 5%</p>

“keratoconjunctivitis sicca” and corneal abrasion³². As a result of the corneal lesion is verified also a phlogistic answer with cytokines release and inflammatory type cells migration. The condition of the tear film, insufficient or nearly absent and also lacking in “nourishing” substances and equipped with anti-inflammatory activity, prevent the normal reepithelization and determine the lesions chronicization. The subjective symptoms are represented by burning sensation, sometimes with pruritus and more rarely with feeling than “eye bathed” not accompanied by epiphora, difficulty to close the eyes, clouded or however variable vision, feeling of foreign body, of “little pebbles in the eyes” or of “sand”, ocular pain in toto and photophobia also very intense, beside the feeling of ocular fatigue.

The clinical signs are evidenced on the conjunctiva and the cornea. The first appears hyperaemic, mainly in the exposed zones; there are present mucine deposits in the lachrymal menisci and, in the more severe cases, chemosis and keratinisation signs are observed.

The corneal signs can be distinguished in initials with epithelial sufferance and filamentous keratitis, or lating with stromal infiltrates, marginal ulcers, “melting” and neovascularisation^{31,32}.

Sjögren's Syndrome Oral Manifestations

Oral Physiology Synthesis

The human salivary flow rate varies in the 24 h, in basal and physiologically normal conditions, from 700-800 ml to a maximum of 1500 ml (1 ml/min approximately), values that correspond to the sum of the basal salivation and the salivary secretions normally stimulated by foods consumption (Table VII). Many factors (endogenous and exogenous) can influence the basal salivary rate entity and so the salivary composition. Between these we can remember the organic hydratation state, the electrolytic equilibrium,

the biorhythms, the body position, the stimulation from various alimentary substances, the anagraphic age.

The salivary composition has an interindividual variability, explained by the fact that the various salivary glands contribute with different compounds and because the final composition is adapted to the stimulus that has evoked the same secretion. Saliva is composed by: water (99.5%), solids (0.5%), 4000-6000 desquamate cells, 2500-6500 leukocytes/ml, 600/700 bacteria/ml. The inorganic salivary fraction is represented by: sodium, potassium, phosphorus, calcium, chlorine, bromine, fluorine and magnesium. The organic salivary fraction is represented by: salivary glucose, salivary amino acids, salivary lipids, blood coagulation factors (agglutinogens A, B, 0), urea, hormones (estrone, testosterone, cortisol, α -hydroxyprogesteron) and salivary proteins: salivary amilases (ptialine), salivary glucoproteins, staterine, proteins rich in prolyl, cystatin, hystamine, sialin, immunoglobulins, lysozyme, lactoferrin, lactoperoxidase, exokynase, lactate dehydrogenase, peroxidase.

- The salivary secretions main functions are:
- Cleansing and washing oral and teeth surfaces;
- Lubricating and hydrating action;
- Saturation and digestive processes;
- Oral and teeth surfaces protection;
- pH and salivary buffer systems;
- Oral microbial flora control;
- Effects on the mineralization;
- Actions on the taste perception;
- Exogenous compounds inactivation.

Xerostomia

The main and evident Sjögren's syndrome oral manifestation is xerostomia. Xerostomia represents a clinical condition characterized by salivary flow rate decrease, with values inferior to 500 ml over a 24-hour period, that recognizes an important variety of causes (Tables VIII and IX). It provokes in the patient a subjective oral dryness sensation, that can be more

Table VII. Symptoms at presentation.

Waking: 16 h	Sleep: 7 h	Mastication: 1 h
Salivary flow rate: 0.3-0.5 ml/min Total produced saliva volume: 300-480 ml	Salivary flow rate: 0.1 ml/min Total produced saliva volume: 40-45 ml	Salivary flow rate: 4 ml/min Total produced saliva volume: 200-250 ml

Table VIII. Long-standing xerostomia responsible factors⁶.

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

or less related with a real dysfunctional state of the salivary glands. The oral dryness sensation can be caused, in determined conditions, by sensory system disorders or conscious function disorders. The subjects affected by an effective salivary glands hypofunction have troubles of high intensity, so intense to compromise their general well-being state and to decrease the quality of life.

Xerostomia gives:

- formation of caries (mainly in correspondence of the cervical teeth zone);
- acute gingivitis;

Table IX. Drugs that may give rise to xerostomia⁶.

<ul style="list-style-type: none"> • Atropine and antimuscarinics • Tricyclic antidepressants • Serotonin reuptake inhibitors • Antihistamines • Antipsychotics • Decongestants • Bronchodilators • Appetite suppressants • Amphetamines • Lithium • Omeprazole • Oxybutynin • Disopyramide • Dideoxynosine • Didanosine • Diuretics • Protease inhibitors

- periodontal disease;
- candidiasis (70% of the cases): acute pseudo-membranous candidiasis, median rhomboid glossitis, denture-associated stomatitis, angular cheilitis);
- dysarthria;
- dysphagia;
- dysgeusia;
- burning tongue/depapillation of tongue;
- oral mucosal soreness;
- dry, sore, cracked lips;
- salivary glands enlargement.

Therapy of Xerostomia

A certain relief of the symptomatology can be obtained advising the patient to adopt some habits:

- Drink frequently;
- Dissolve small ice cubes in the mouth;
- Apply on the dry lips emollients and moisturizing creams;
- Avoid the use of alcoholic substances with a dehydrating effect on the mucus membranes (alcohol, coffee, tea);
- Humidify the living medium air with humidifiers;
- Have a semiliquid diet, avoiding dry or with a certain consistency foods;
- Prefer drugs administration with liquid formulations.

To assure the oral mucus membranes humidifying and lubrication, different substances can be advised and/or prescribed:

- Aspecific sialogogues: sweets with citric acid and without monosaccharides, chewing gums sweetened with sorbitol or xylitol and enriched with enzymes as lactoperoxidase and glucose oxidase;
- Salivary substitutes: artificial saliva with methylcellulose or mucin and fluorine, moisturizing gels with enzymes as lactoperoxidase, lysozyme, glucose oxidase, lactoferrin. Systemic sialogogues drugs.

In literature, there are indicated different salivary stimulation methods⁶:

- The use of toothpastes, mouthwashes and chewing gums with salivary enzymes and fluorine;
- The electrostimulation;

- The acupuncture;
- The use of vitamin supplementation;
- The use of primrose oil (rich in fatty acids, it inhibits two series of prostaglandins with the increase of the salivary flow in some individuals with Sjögren's syndrome);
- Coffee chewing;
- The use of saline linen extract, with or without chlorhexidine.

Pharmacologic Therapy in the Management of Sjögren's Syndrome

The pharmacologic therapy is based mainly on the administration of direct cholinergic drugs (pilocarpine, bethanechol, carbachol).

The direct cholinergic drugs, or muscarinic drugs, reproduce the acetylcholine effect binding directly on M-type receptors (muscarinic receptors).

The muscarinic receptors are localized in the organs innervated by the parasympathetic autonomous nervous system and in the central nervous system (CNS). They are distinguished in five subclasses, of which only the first three are important from the pharmacologic point of view (M1, M2, M3), all belonging to the G-protein coupled receptors family (regulation proteins localized on the internal side of the cellular membrane, with intrinsic GTP-ase activity)³³⁻³⁶.

M1 and M3 receptors activate through a G-protein, the C phospholipase (enzymatic effector that hydrolyzes a membrane phospholipid, the phosphatidylinositol) from which derives the formation of inositol and diacylglycerol, as second messengers, and the liberation of Ca⁺⁺ ions from the intracellular deposits. Ca⁺⁺ ions bind to a protein, the calmodulin, that activates various enzymes and starts different biological answers, as the smooth muscles contraction, the exocrine glandular secretion, etc.

M3 receptors are localized on smooth muscles, exocrine glands and endothelial cells, where have essentially exciting effects.

The muscarinic drugs have in comparison with the physiological agonist, a certain resistance to the acetylcholinesterase, allowing a more lasting action. These drugs provoke an indiscriminating stimulation of the muscarinic receptors, without any specificity for the different organs and their administration is followed therefore by various side effects. This drug class has two main

groups: the natural alkaloids and the choline's esters. The only natural alkaloid of clinical interest is the pilocarpine, that will be treated later on.

The choline's esters (bethanechol, carbamechol) maintain the acetylcholine characteristics, important for the bond to the receptor, as a quaternary ammonium group positively charged and an estheric group, opportunely modified to made it less sensible to acetylcholinesterases hydrolysis.

The use of direct cholinergic drugs requires caution because they have various side effects: bradycardia, hypotension, bronchoconstriction, bronchial hypersecretion, sweating, diarrhoea.

The systemic absorption for high doses exposes to the risk of cholinergic crisis.

Systemic Sialogogues Drugs

Pilocarpine Hydrochloride

Pilocarpine hydrochloride is a tertiary amine derived from *Pilocarpus pennatifolius* leaves, stable to the cholinesterase hydrolysis³³, with acetylcholine M3 muscarinic receptors parasympathetic agonist action, and mild β -adrenergic activity.

This natural alkaloid provokes the exocrine glands pharmacologic stimulation (salivary, sweat, lachrymal and respiratory mucous glands), the smooth muscles contraction, and the motility of the gastrointestinal and urinary tracts, gall bladder, biliary ducts and bronchi. The use of this drug as a sialogogue date to the early 1800s, when Brazilians who worked in the fields, chewing *Pilocarpus jaborandi* leaves, observed an increase in flow of saliva. This discovery prompted the Brazilian physician Coutinho, to introduce *Pilocarpus jaborandi* in the treatment of oral dryness³⁷.

In 1967, begins the drug experimentation in clinical trials, and its sialogogue action is confirmed with salivary flow improvements in patients with Sjögren's syndrome³⁷.

Pilocarpine is readily absorbed by the gastrointestinal tract, and peak plasma concentrations are reached within approximately 1 hour. It is metabolized by the liver and excreted principally by means of the kidneys, with an elimination half-life of approximately 1 hour⁶.

Systemic pilocarpine increases exocrine glands secretion and it can also give rise to adverse effects, that reflects its other cholinergic actions.

The side effects are^{6,37}: sweating, headache, nausea, mild abdominal pain, urinary frequency, flushing and influenza-like symptoms, rhinitises, increased lacrimations, palpitations, tachycardia, bradycardia, increased pulmonary secretions, increased smooth muscle tone and blurred vision.

Pilocarpine is contraindicated in the case of gall bladder diseases, glaucoma, acute iritis, and renal colic. Risk to the patient must be evaluated when administrating pilocarpine to patients with heart diseases, asthma, angina pectoris, chronic bronchitis, chronic obstructive pulmonary diseases or history of myocardial infarction. There are possible the interaction of pilocarpine with β -adrenergic antagonists (i.e. in the patients under therapy with β -blockers antihypertensive drugs⁶) and other parasympathomimetic drugs such as edrophonium chloride, bethanechol chloride and yohimbine hydrochloride (Table X)³⁷.

In the management of Sjögren's syndrome, pilocarpine must be administrated with a dosage of 5 mg (1 hour before eating³⁷), 4 times daily for at least 12 weeks. The onset time is approximately 30 minutes and the duration of action is approximately 2-3 hours⁶.

The therapy with pilocarpine reduces the frequency of oral and ocular symptoms related to xerostomia and xerophthalmia and the oral carriage of *Candida Albicans* in Sjögren's syndrome, thanks to the pharmacologically induced salivary flow increase^{6,38}.

Cevimeline Hydrochloride

Cevimeline is a quinuclidine (analog of acetylcholine) with a high affinity for M3 muscarinic receptors both of lachrymal and salivary glands (a 40-fold greater affinity for M3 receptors than does pilocarpine) and a low affinity for M2 receptors on cardiac and lung tissue. This cholinergic

agonist was approved by the US FDA (Food and Drug Administration) in 2000 for the treatment of xerostomia in patients with Sjögren's syndrome.

The recommended dosage is 30 mg, 3 times daily. The reported peak blood concentration is 1.5 to 2 hours, with a half-life of 5 ± 1 h³⁷.

To this dosage, cevimeline increases the salivary flow and improves the subjective and objective symptoms of patients with xerostomia associated to Sjögren's syndrome. The drug is metabolized principally by the liver and it is excreted through the kidneys.

When is used with a dosage of 60 mg, 3 times daily, although providing symptomatic relief, it was observed an increase of the adverse effects, particularly gastrointestinal tract disorders⁶.

Cevimeline, having as a more specific target the salivary glandular tissue, should be characterized by less severe side effects than pilocarpine. These include: sweating, gastrointestinal upset, urinary frequency and visual disturbances³⁷. It has been suggested that patients with a controlled hypertension, could tolerate cevimeline better, but it must be applied the same contraindications of pilocarpine.

Cevimeline is contraindicated in patients with uncontrolled asthma, glaucoma or acute iritis. It may alter cardiac conduction and heart diseases may not be able to compensate these transient hemodynamic changes.

The drug must be administrated with caution in patients with asthma, chronic bronchitis, chronic obstructive pulmonary disease or cardiovascular diseases³⁷.

Bethanechol Chloride

Bethanechol is the β -methylcholinic ester of carbammic acid, which has both muscarinic and nicotinic agonist action⁶. This cholinergic drug is commonly used in the clinical practice to stimulate the bladder emptying in post-operative and post-partum urinary holding and in the bladder neurogen atrophy. It can be used also as sialogogue, because it stimulates the parasympathetic autonomous nervous system, with a subsequent release of acetylcholine at the nervous endings and so production of saliva from the salivary glands.

Administrated to patients in therapy with tricyclic antidepressants to alleviate the anticholinergic side effects (xerostomia, constipation and bladder inhibition) in doses of 25 mg, 3 times daily, for oral administration, confers a sympto-

Table X. Sialogogue drugs proposed by Grisius³⁷.

<ul style="list-style-type: none"> • Pilocarpine • Cevimeline • Bethanechol • Anethole • Guaifenesin • Bromhexine • Herbal medications • Neostigmine • Yohimbine • Potassium iodide • Nicotinic acid • Malic acid • Vitamin A

matology improvement³⁷. Administrated with the same dosage to patients with xerostomia secondary to radiations, it was observed a stimulated and unstimulated salivary flow increase, but the objective changes of the salivary flow not always are associated to symptomatic improvements⁶. It was documented the case of a patient in therapy with phenothiazide, to which was administrated bethanechol, how he reported a decrease in oral dryness.

The bethanechol dosage for gastrointestinal effects according to Grisius³⁷ is 10-50 mg, 4 times daily. Through oral administration, the onset time is 30 minutes with the maximum effectiveness at 60 to 90 minutes. The duration of action is 1 hour, although larger doses (300-400 mg) produce gastrointestinal effects for 6 hours.

The cholinergic side effects are: gastrointestinal upset, sweating and miosis. The cardiovascular effects include decreased blood pressure, with reflex tachycardia and were reported also bronchial obstruction and asthmatic attacks.

The contraindications include patients with bronchial asthma, hyperthyroidism, peptic ulcer disease, bradycardia, hypotension, mechanical obstruction and compromission of the gastrointestinal and urinary tracts.

Anethole-Trithione

Anethole-trithione is a drug with cholinergic effect³⁷, because it increases the availability of muscarinic receptors on the postsynaptic membrane and thus enhances the potential for cholinergic stimulation⁶. The drug may act directly on the secretory cells of the salivary glands with salivation stimulation and xerostomia improvement.

Anethole-trithione is administrated in doses of 25 mg, 3 times daily. It is metabolized primarily by the kidneys. Its major reported side effect is gastrointestinal upset with flatulence. The drug can intensify the salivation induced by pilocarpine in patients with radiation-induced xerostomia, but it may not be of benefit in the management of primary Sjögren's syndrome.

This drug is not available in the United States.

Carbachol (Carbamylcholine)

Carbachol is a choline ester with a strong action, both on muscarinic and nicotinic receptors, and with a long duration action, reason for which it is rarely used in therapy, except that as miotic agent to reduce the endocular pressure in glaucoma³³. This drug could be useful in the radiation-

induced xerostomia therapy, but there are still not present definitive results in literature on this purpose⁶.

Pyridostigmine

Pyridostigmine is an indirect cholinergic drug, more precisely an anticholinesterasic with a medium range of action, derived from the quaternary ammonium. Pyridostigmine and neostigmine (also derived by the quaternary ammonium) found wide use in the clinical practice because thanks of their polarity, they doesn't penetrate into the central nervous system (CNS). For their effect on the parasympathetic autonomous nervous system, they are used to stimulate the intestinal and bladder smooth muscles in the neurogen or postoperative atony cases while for the effects on the neuromuscular junction they are employed in the therapy of myasthenia gravis and as antidotes of the competitive curares³³.

The data available in literature suggest that the use of pyridostigmine may be of benefit in the treatment of drug-related xerostomia, but there are still no data on the efficacy of this agent in the management of other diseases that give rise to xerostomia⁶.

Bromhexine

Bromhexine is an alkaloid derived from *Adhatoda vasica*, used as mucolytic agent in the treatment of chronic bronchitis and obstructive pulmonary disease, that acts by increasing the quantity of secretions while decreasing their viscosity³⁷. Several clinical studies evaluated the use of bromhexine in patients with Sjögren's syndrome. On the basis of the published data, this drug does not appear to be indicated for the treatment of xerostomia.

Mucolytic Agents

Some mucolytic agents as guaifenesin and potassium iodide, used in the respiratory infections treatment, are able to decrease the saliva viscosity and improve the symptoms of oral dryness through the optimization of the salivary flow through the salivary ducts.

Alpha Interferon (α -IFN)

The interferon is an antiviral proteic substance produced by various cells, that inhibits the viruses reproduction. Its production is active, although in a minor quantity, also in cells non-invaded by viruses. Alpha interferon has a function mainly antiviral and thanks to the ge-

netic engineering techniques, today is produced at a cost relatively low and on large wide. In the USA it was used in the treatment of hepatitis, AIDS-related Kaposi's sarcoma, melanoma and various carcinomas³⁹.

Alpha interferon has significant side effects, including hepatotoxicity, fatigue, anorexia, central nervous system complications and psychiatric disorders³⁷. In vitro α -IFN increases the transcription and production of aquaporin-5, a membrane-bound protein complex important in lachrymal and salivary gland functions⁶.

In literature there are controversial results about the use of α -IFN in the management of Sjögren's syndrome, because while it is suggested that the parenteral use of α interferon increases the salivary and lachrymal flow of patients with primary and secondary Sjögren's syndrome⁶, seems that systemic α -IFN gives rise to a wide range of side effects, including xerostomia and the same Sjögren's syndrome, because it is involved as a pro-inflammatory cytokine relevant in the pathogenesis of Sjögren's syndrome³.

Hydroxychloroquine

Hydroxychloroquine is an antimalarial drug with anti-inflammatory properties used in the treatment of rheumatoid arthritis and systemic lupus erythematosus³⁷. This drug may be of some clinical benefit at dosages of 6-7 mg/kg/day, producing a reduction in serum IgG and IgM levels and C-reactive protein and erythrocyte sedimentation rate (ESR) and a fall in salivary levels of IL-6, in Sjögren's syndrome, without causing significant retinopathies⁶.

Actually, hydroxychloroquine is recommended for the treatment of extraglandular manifestations of Sjögren's syndrome^{1,3,4,6,37}.

The drug side effects are: dermatologic reactions, chloroquine retinopathy (a potential irreversible dose-related side effect) that occurs within several months or years of daily therapy, hematic dyscrasias (aplastic anemia, leukopenia and thrombocytopenia), nervousness, emotional changes, skeletal muscle weakness, nausea and vomiting³⁷.

Corticosteroids

Although in literature there are controversial results about systemic corticosteroids effectiveness in reducing ocular and oral symptoms in Sjögren's syndrome⁶, some data report that prednisolone in doses of 30 mg in alternate days, was able to improve these symptoms. Finally, the irri-

gation of the salivary major glands with a solution of prednisolone 2 mg/ml in saline solution improved acetylcholine-induced sweating in a patient with anhidrosis related to Sjögren's syndrome⁶.

Other Drugs Examined in Literature

Different studies^{4,6,37} examined the literature about the use of some anti-inflammatory non steroids drugs, methotrexate, cyclosporine, cyclophosphamide, azathioprine, sulfalazine and thalidomide in the management of Sjögren's syndrome, but from results emerged that no one of these drugs demonstrated a real improvement of the syndrome clinical features.

Anti-TNF (Anti-Tumour Necrosis Factor) Drugs

Infliximab is a recombinant anti-tumour necrosis factor antibody agent, that was studied in patients with primary Sjögren's syndrome, being administrated in doses of 3 mg/kg at 0, 2 and 6 weeks. There was observed an improvement in the clinical and functional parameters, mainly of the ESR and of the salivary and lachrymal flow rate. The improvement was maintained only for a period of approximately 1 year from the drug administration interruption⁴. Further studies are necessary to demonstrate a favourable risk/benefit ratio of the drug in its use in the therapy of Sjögren's syndrome.

Rituximab is an anti-CD 20 antibody agent. It is known that the B-cells activation with hypergammaglobulinaemia is one of the main features of the pathogenesis of Sjögren's syndrome⁴, therefore anti-B-cell antibodies should have a therapeutic effect in the syndrome features.

Administrated in the therapy of a B-cell lymphoma in a patient with Sjögren's syndrome, demonstrated the regression of the tumour and an important improvement in the Sjögren's syndrome in the same individual⁴. So, as in the case of infliximab, further studies are necessary to confirm the drug effectiveness and validity in the therapy of Sjögren's syndrome.

Conclusions

Sjögren's syndrome therapy is palliative. It doesn't exist a resolutive treatment of the disease. The therapeutical approach is in fact turned

to the treatment of xerostomia and xerophthalmia. Xerostomia can be treated through the administration of systemic sialogogue drugs, aspecific sialogogues and salivary substitutes. Of primary importance results the prevention of the oral xerostomia complications, through the maintenance of an optimal domiciliary oral hygiene, frequent dental visits and the adoption of behaviours as avoiding the consumption of foods sweetened with saccharose.

Particularly useful results the topical application of fluorine in the prevention of caries. Oral candidiasis, a frequent complication, necessitates of an adequate antimychothic treatment.

The syndrome prognosis is complicated by the possible lymphomatous degeneration that is verified in 5% of the cases and it is frequent in patients with primary Sjögren's syndrome.

The management of the patient affected by Sjögren's syndrome must be actuated through the collaboration of three professional figures, as the dentist, the oculist and the rheumatologist.

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