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French national diagnostic and care protocol for Sjögren's disease

Protocole national de diagnostic et de soins –

Maladie de Sjögren

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1. Abbreviations

ACPA = anti-citrullinated protein antibody; AFGS = French Association for Gougerot-Sj ogren and Sicca syndromes; AHAI = autoimmune haemolytic anaemia; AIR = autoimmunity and rituximab b; ALT = alanine aminotransferase; ANCA = anti-neutrophil cytoplasmic antibody; AST = aspartate aminotransferase; AVB = auriculo-ventricular block; cAVB = congenital auriculo-ventricular block; BAFF = B-cell activating factor; BTK = Bruton's tyrosine kinase; CBC = complete blood count; CIDP = chronic inflammatory demyelinating polyradiculoneuritis; CNS = central nervous system; CPK = creatinine phosphokinase; CRAT = Reference Centre on Teratogens; CRP = C-reactive protein; CT = computed tomography; DEQ = Dry Eye Questionnaire; DLBCL = diffuse large B-cell lymphoma; DLCO = diffusing capacity of the lung for carbon monoxide; DMARD = disease modifying anti-rheumatic drug; ECG = electrocardiogram; EMG = electromyogram; ENT = Ear, Nose, Throat; ESMO = European Society for Medical Oncology; ESSDAI = Eular Sj ogren's Syndrome Disease Activity Index; ESSPRI = Eular Sj ogren's Syndrome Patient Reported Index, FGFR = fibroblast growth factor receptor; FVC = forced vital capacity; GA = Gestational Age; G-CSF = granulocyte colony-stimulating factor; GFR = glomerular filtration rate; HAS = French National Authority for Health; HBV = hepatitis B virus; HCQ = hydroxychloroquine; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IFN = interferon Ig immunoglobulin; IL = interleukin; ILD = interstitial lung disease; ITP = immune thrombocytopenia; JAK = janus kinase; LDH = lactate dehydrogenase; LGL = large granular lymphocytes; LTC = long-term condition; MA = marketing authorisation; MALT = mucosa-

associated lymphoid tissue; MRI = magnetic resonance imaging; NDCP = national diagnostic and care protocol; NIBUT = non-invasive break-up time; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; NSAID = non-steroidal anti-inflammatory drug; NSIP = non-specific interstitial pneumonia; OCT = optical coherence tomography; OP = organising pneumonia; OSDI = Ocular Surface Disease Index; OSS = Ocular Staining Score; PDGFR = platelet derived growth factor receptor; PET = positron emission tomography; LIP = lymphoid interstitial pneumonia; PFT = pulmonary function testing; SANDE = Symptom Assessment in Dry Eye⁴²⁴; SD = Sjögren's disease; SF36 = Short Form 36; SFN = small fibre neuropathy; SS = Sjögren's syndrome; STAT = signal transducer and activator of transcription; TPE = therapeutic patient education; UIP = usual interstitial pneumonia; VAS = Visual Analogue Scale; VEGFR = vascular endothelial growth factor receptor; TATA= TArgeted Therapy in Auto-immune diseases; TNF = tumour necrosis factor; TSH = thyroid-stimulating hormone; γ GT =gamma-glutamyl transpeptidase.

a b s t r a c t

Sjögren's disease (SD), also known as Sjögren's syndrome (SS) or Gougerot-Sjögren's syndrome in France, is a rare systemic autoimmune disease in its primary form and is characterised by tropism for the exocrine glandular epithelia, particularly the salivary and lacrimal glands. The lymphocytic infiltration of these epithelia will clinically translate into a dry syndrome which, associated with fatigue and pain, constitutes the symptom triad of the disease. In about one third of patients, SD is associated with systemic complications that can affect the joints, skin, lungs, kidneys, central or peripheral nervous system, and lymphoid organs with an increased risk of B-cell lymphoma. SD affects women more frequently than men (9/1). The peak frequency is around the age of 50. However, the disease can occur at any age, with paediatric forms occurring even though they remain rare. SD can occur alone or in association with other systemic autoimmune diseases. In its isolated or primary form, the prevalence of SD is estimated to be between 1 per 1000 and 1 per 10,000 inhabitants. The most recent classification criteria were developed in 2016 by EULAR and ACR. The course and prognosis of the disease are highly variable and depend on the presence of systemic involvement and the severity of the dryness of the eyes and mouth. The current approach is therefore to identify at an early stage those patients most at risk of systemic complications or lymphoma, who require close follow-up. On the other hand, regular monitoring of the ophthalmological damage and of the dental status should be ensured to reduce the consequences.

Résumé

La maladie de Sjögren (MS), aussi appelée syndrome de Sjögren primitif et, en France, syndrome de Gougerot-Sjögren, est une maladie auto-immune systémique rare dans sa forme primaire et se caractérise par un tropisme pour les épithéliums glandulaires exocrines, en particulier les glandes salivaires et lacrymales. L'infiltration lymphocytaire de ces épithéliums

se traduira cliniquement par un syndrome sec qui, associé à la fatigue et à la douleur, constitue la triade symptomatique de la maladie. Chez environ un tiers des patients, la MS s'accompagne de signes systémiques avec atteinte possible des articulations, de la peau, des poumons, des reins, du système nerveux central ou périphérique et des organes lymphoïdes, avec un risque accru de lymphome B. La MS touche plus fréquemment les femmes que les hommes (9/1). Le pic de fréquence se situe vers l'âge de 50 ans. Cependant, la maladie peut survenir à tout âge, avec des formes pédiatriques même si elles restent exceptionnelles. La MS peut survenir seul ou en association avec d'autres maladies auto-immunes systémiques. Dans sa forme isolée ou primaire, la prévalence de la MS est estimée entre 1 pour 1000 et 1 pour 10 000 habitants. Les critères de classification les plus récents ont été développés en 2016 par l'EULAR et l'ACR. L'évolution et le pronostic de la maladie sont très variables et dépendent de la présence d'une atteinte systémique et de la sévérité de la sécheresse oculaire et buccale. L'attitude actuelle est donc d'identifier à un stade précoce les patients les plus à risque de complications systémiques ou de lymphome, qui nécessitent un suivi étroit. D'autre part, un suivi régulier des atteintes ophtalmologiques et de l'état dentaire doit être assuré pour en réduire les conséquences.

2. Summary for the attending physician

Sjögren's disease (SD) or Sjögren's disease (SD) is a systemic autoimmune disease classified as a rare disease. Its prevalence is estimated to be between 1/1000 and 1/10,000. Every general practitioner will be confronted with this disease in his or her career. The delay between the onset of symptoms and the diagnosis is often long and the role of the general practitioner is crucial for an early diagnosis.

In addition, the symptom triad of dryness, fatigue and joint pain is so common in the general population that, as a general practitioner, you will ask yourself about Sjögren's disease in many situations.

Most often, when faced with this triad, you will not find a clear organic disease and you will make a diagnosis of polyalgic syndrome (sometimes called fibromyalgia) or idiopathic sicca syndrome. You know better than any other physician about the intertwining of psychological factors in these symptoms. It is important to remember that the sicca syndrome can be part of the fibromyalgia syndrome even in the absence of psychotropic medication that causes dryness.

When confronted with this triad, you will suggest Sjögren's disease according to associated elements:

- 90% of cases are women, often around the age of 50;
- the pain is restricted to the limbs and more specifically to the joints and muscles. They are often inflammatory in nature;
- dry mouth and/or eyes are disabling, requiring the patient to drink at night and often to apply lubricating eye drops;
- finally, there are associated symptoms that may suggest systemic involvement.

Indeed, in 30–40% of cases there are systemic effects of the disease. The most frequent is the existence of a history of parotid or submaxillary swelling. In young subjects (because the disease can also affect young subjects), the mother will tell you “he/she has had mumps several times. . .”. The joint pain may be accompanied by real episodes of polyarthritis-like swelling, as in rheumatoid arthritis. Skin signs can be found, mainly purpura. Bronchial or pulmonary signs, adenopathies, peripheral neurological signs such as sensory disorders or even motor deficits are also reported. Finally, Sjögren’s disease may be primary or associated with another known systemic autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma or inflammatory myopathies.

The main systemic complication is the occurrence of lymphoma, which is about 10 times more frequent than in the general population. However, the patient should be reassured as its frequency remains low: 5% of patients. Risk factors are now well-known: the presence of moderate or severe systemic disease activity, frequent episodes of parotidomegaly, purpura and the presence of mono-clonal immunoglobulin and rheumatoid factor on laboratory test results. In the absence of these risk factors, there is no increased risk of lymphoma.

When you suspect Sjögren’s disease, the first diagnostic step is to carry out an antinuclear antibody test (which must be carried out on cells transfected with Ro-60/SSA) with specificity tests for anti-SSA/Ro60 and anti-La/SSB. In this immunological work-up, you will add rheumatoid factor testing, which is positive in 50% of cases, i.e. almost as often as in rheumatoid arthritis, but without anti-citrullinated peptide antibodies (ACPAs), and protein electrophoresis to test for polyclonal hypergammaglobulinaemia.

If these laboratory tests are negative, this does not eliminate the diagnosis: 30% of patients with Sjögren’s disease do not have detectable autoantibodies and the diagnosis is made on the basis of a biopsy of the accessory salivary glands (which should be carried out in an expert centre). In this case you will refer the patient to a specialist who is usually a rheumatologist or internist or to a centre of competence or reference.

The treatment of this disease remains difficult even though many molecules are being tested. There is no drug that can treat all aspects of the disease. Unlike lupus, hydroxychloroquine (HCQ) is not routinely given, as it does not alter the course of the disease. However, the various systemic complications must be diagnosed and can be treated by immunomodulators or immunosuppressants (methotrexate, leflunomide, rituximab, mycophenolic acid. . .). Corticosteroids are most often ineffective in treating the pain in this disease (except for purely joint pain) and should only be given as a very short course of treatment (2 to 5 days) for

painful parotids swelling or in the event of a systemic complication after consulting a specialist doctor. Finally, it is important to know that pilocarpine, a little-known drug, has good efficacy on the sicca syndrome, mainly dry mouth. It is not easy to prescribe in France because there is only one speciality: Salagen*, which is not reimbursed and which does not allow the treatment to be started in progressive doses. Pilocarpine hydrochloride can be prescribed in the form of compounded capsules, which are most often reimbursed. However, in France, this reimbursement is left to the discretion of the regional health insurance funds. Other galenic preparations contain pilocarpine and can be offered to the patient (by referring to the centre of competence or reference).

Finally, dryness in Sjögren's disease is not only oral (xerostomia) and ocular (xerophthalmia), it is also cutaneous, bronchial and vaginal. As the disease primarily affects women, the issue of vaginal dryness should be discussed with the patient. As mentioned above, pilocarpine may be helpful as well as local treatments to be discussed with the gynaecologist. The presence of a vaginal dryness syndrome may be an argument for offering a woman over 50 years old a hormone replacement therapy which may have a positive effect on this symptom. This serves as a reminder that Sjögren's disease does not contraindicate oestrogenic contraception, which is completely possible. Pregnancy does not aggravate disease progression and is possible at any time the patient decides, except in case of a severe systemic attack. In the presence of anti-SSA antibodies, there is a very small risk of cardiac conduction disorders such as atrioventricular block in the foetus (< 2%) and skin disorders in the newborn (5%), which justifies a preconception consultation and management in a maternity hospital accustomed to autoimmune diseases.

In conclusion, your role as an attending physician is crucial as in any chronic disease. It is important to remember that there is still no cure for this disease but many treatments can relieve and treat most of the symptoms and complications. It is important to reassure the patient that the disease has no impact on his or her life expectancy in the absence of systemic complications, that the risk of lymphoma is rare, that the patient can lead a strictly normal life as a woman, including pregnancy, and that there is no risk of blindness despite the permanent discomfort in the eyes, which often leads to blurred vision. It is also important to follow-up on possible complications of Sjögren's (through clinical and laboratory testing), to monitor oral health, to offer the patient advice from a centre specialised in this rare disease and to offer patients the opportunity to be included in current or future therapeutic trials.

In this French National Diagnostic and Care Protocol (NDCP), we try to give you the keys to a better understanding of this disease, the data from Orphanet and the contact details of the patient associations which are very helpful, as in all chronic diseases, and very involved in the therapeutic education programmes which are very useful and appreciated by patients.³

3.Introduction [1–14]

3.1. Definition Sjögren's disease

(SD) is a rare systemic autoimmune disease in its primary form and is characterised by tropism for the exocrine glandular epithelia, particularly the salivary and lacrimal glands. The lymphocytic infiltration of these epithelia will clinically translate into a sicca syndrome which, associated with fatigue and pain, constitutes the symptom triad of the disease.

In France, the disease is often referred to as Gougerot-Sjögren syndrome. Gougerot had described the oral form of the disease some years before Sjögren but it was Sjögren who linked the sicca syndrome to the systemic signs and the name of the Parisian dermatologist has disappeared from the definition of the disease except in France. In any case, proper nouns are never the best way to describe a disease and the best acronym would be the term autoimmune epithelitis which perfectly explains the role of the epithelia in attracting autoimmune lymphocytes. Finally, recently the term “syndrome”, which is too vague, has been usefully replaced by the term “disease”, which reminds us that the framework that describes this disease is perfectly defined.

In about one third of patients, SD leads to systemic complications that can affect the joints, skin, lungs, kidneys, central or peripheral nervous system, and lymphoid organs with an increased risk of B-cell lymphoma.

3.2. Epidemiology

SD affects women more frequently than men, with a sex ratio of 9 women to 1 man. The peak frequency is around the age of 50. However, the disease can occur at any age, with paediatric forms occurring even though they remain rare. SD can occur alone or in association with other systemic autoimmune diseases, the most common being rheumatoid arthritis, but also lupus or scleroderma. In its isolated or primary form, the prevalence of SD is estimated to be between 1 per 1000 and 1 per 10,000 inhabitants.

3.3. Pathophysiology

SD is multifactorial in origin. Studies comparing identical and fraternal twins show that there is a contribution from both genetic and environmental factors. The role of an infectious trigger (bacterial and/or viral) has long been suspected, although no specific infectious agent has been found as a clear explanation. More recently it has been suspected that abnormal expression of endogenous retroviral sequences may lead to the activation of epithelial cells and the innate and adaptive immune system. The existence of polymorphisms, particularly in genes involved in the interferon (IFN) response, could foster this excessive immune system response.

Different immune players have been identified. The IFN signature (type I or II) is present in more than 50% of patients in blood and target tissues (salivary glands). This increase in IFN

will result in the excessive production, particularly by epithelial cells, of the cytokine BAFF (B-cell activating factor), which stimulates the survival, proliferation and maturation of B lymphocytes. B lymphocyte hyperactivation is a feature of SD. It is reflected in the presence of autoantibodies (anti-SSA, anti-SSB, rheumatoid factor), hyper-gamma globulinaemia and ectopic germinal centres in the salivary glands. The presence of circulating plasma blasts and plasma cells infiltrating the salivary glands is part of the cellular signature of SD, which also includes the presence of activated T cells. The IFN signature and B or T lymphocyte hyperactivation are therefore currently being explored as therapeutic targets in this disease.

Table 1
ACR-EULAR classification criteria for Sjögren's disease.

Items	Weight
Biopsy of the accessory salivary glands with lymphocytic sialadenitis and focus score ≥ 1	3
Presence of anti-SSA/Ro	3
Ocular Staining Score ≥ 5 (or Van Bijsterveld score ≥ 4) in at least 1 eye	1
Schirmer's test ≤ 5 mm/5 min in at least 1 eye	1
Unstimulated salivary flow ≤ 0.1 mL/min	1

Sjögren's disease if total score ≥ 4

These criteria apply ONLY IF the patient has: At least 1 symptom of dry eyes or dry mouth: Ocular symptoms (at least one of three listed below): Have you had troublesome and persistent dry eyes daily for more than 3 months?, Do you have a recurring feeling of sand or gravel in your eyes?, Do you use artificial tears more than 3 times per day?; Mouth symptoms (at least one of three listed below): Have you had the sensation of dry mouth daily for more than 3 months?, Do you have persistent or recurrent salivary gland swelling as an adult?, Do you often use liquids to help you swallow solid foods?; Or a suspicion of SD based on EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) score > 0 . Exclusion criteria – History of: Head and neck irradiation; Active hepatitis C (defined as positive PCR); HIV-related illness; Sarcoidosis; Amyloidosis; Graft versus host disease; IgG4-associated disease; NB: a history of lymphoma is no longer an exclusion criterion.

3.4. Classification

The most recent classification criteria were developed in 2016 by EULAR and ACR and are weighted. According to these criteria, the diagnosis of SD is based on the presence of an objective immuno-logical abnormality: either anti-SSA antibodies (only Ro60 and not Ro52; and no consideration of anti-SSB), or a biopsy of the accessory salivary glands with a lymphocytic infiltrate assessed by a focus score greater than or equal to 1. A focus score of 1 corresponds to the presence of a cluster of 50 lymphocytes in 4 mm² of glands examined; a Chisholm score of 3 or more is equivalent to a focus score of 1 or more. These criteria are presented in Table 1

3.5. Course and prognosis

The course and prognosis of the disease are highly variable and depend on the presence of systemic involvement and the severity of the dryness of the eyes and mouth. The current approach is therefore to identify at an early stage those patients most at risk of systemic complications or lymphoma, who require close follow-up. On the other hand, regular

monitoring of the ophthalmological damage (risk of disabling keratitis) and of the dental status should be ensured to reduce the consequences.

At present, it is established that patients with a more active immunological profile are more likely to develop systemic complications. This active immunological profile is defined by the positivity of autoantibodies (anti-SSA/Ro60, anti-SSB, rheumatoid factor and especially cryoglobulin) and complement consumption. All these parameters can be assessed in routine clinical practice.

In patients without systemic involvement, the disease is not

associated with a reduction in life expectancy but the impact on quality of life is significant. Regular monitoring of dental status and xerophthalmia is important, particularly because of the high risk of caries and visual impairment in cases of severe dryness.

Excess mortality exists in patients with the most active forms of the disease. The main risk factors for mortality identified are the presence of the immunological factors mentioned above, plus the existence of lymphopenia and active disease as defined by the ESSDAI.

4.Objectives of the French National Diagnostic and Care Protocol

The aim of this French National Diagnostic and Care Protocol (NDCP) is to explain the current optimal diagnostic and therapeutic management and care pathway of a patient with SD to the professionals concerned. The goal is to optimise and harmonise the management and follow-up of the rare disease throughout the country. It also makes it possible to identify pharmaceutical specialities used in an indication not provided for in the Marketing Authorisation (MA) as well as specialities, products or services necessary for the care of patients but not usually covered or reimbursed.

This French NDCP can be used as a reference by the attending physician (the physician designated by the patient to the French National Health Insurance) in consultation with the specialist physician, particularly when drawing up the treatment protocol in collaboration with the consulting physician and the patient, in case of a request for exemption from co-payment for an off-list condition.

However, the French NDCP cannot consider all specific cases, all comorbidities or complications, all therapeutic particularities, all hospital care protocols, etc. It does not claim to cover all possible management approaches, or replace the individual responsibility of the physician towards his or her patient. The protocol does, however, describe the standard management of a patient with Sjögren's disease. It should be updated according to new validated data.

This French NDCP has been drafted according to the “Method for drafting a national diagnostic and care protocol for rare dis-eases” published by the French National Authority for Health (HAS) in 2012 (methodological guide available on the HAS website :<http://www.has-sante.fr>).

5. Diagnosis and initial assessment [1,3–42]

5.1. Objectives

The main objectives, when faced with a patient reporting manifestations that may suggest the diagnosis of SD, are:

- establishing the diagnosis;
- eliminating differential diagnoses;
- searching for visceral damage and assessing its activity;•assessing risk factors for non-Hodgkin’s lymphoma;
- assessing the oral, dental, ophthalmological and gynaecological impact of dryness;
- evaluating the impact of symptoms on quality of life (pain, fatigue, dryness, etc.).

5.2. Professionals involved (and coordination arrangements)The professionals most often involved are:

- the attending physician;
- the specialist physician with expertise in SD, usually a rheumatologist or internist;•the dental surgeon/oral surgeon
- the ophthalmologist;
- the ear, nose, and throat (ENT) specialist;
- the organ specialist depending on the site of the damage (gynaecologist, dermatologist, pneumologist, neurologist, cardiologist, nephrologist, haematologist, psychiatrist, etc.);
- nurses who provide care, therapeutic education and potentially coordination of care between the hospital and the community;
- physiotherapists and occupational therapists who play a role in the management of chronic joint damage;
- the orthoptist for blink training;
- the psychologist or psychiatrist if the psychological impact is significant;
- social workers who play an important role in dealing with the medium and long-term social consequences of the disease.

5.3. Circumstances of discovery/Suspicion of diagnosis

SD is characterised by a strong female predominance (9/1) with a peak in frequency around the age of 50. However, it can also affect younger patients and even children. It may initially present in different forms (dry eyes and mouth, pain, asthenia, swollen salivary glands, visceral damage)

.It is considered primary when it is isolated, and secondary (or rather associated) when it is found in association with another systemic autoimmune disease, such as rheumatoid arthritis, systemic lupus, systemic scleroderma or inflammatory myopathies. A rare but dreaded, or even revealing, complication is the occurrence of non-Hodgkin's malignant lymphoma, usually after several years of evolution but sometimes early on.

Although the diagnosis should be suggested in case of any dry-ness of the eyes and mouth, but also of the skin or vagina, it should be kept in mind that this symptom is very frequent as age advances (less than 5% before the age of 40, its prevalence increases by about 10% per decade after the age of 60, i.e. about 30% of elderly subjects) and that SD is therefore only rarely the cause. Roughly speaking, if 10% of the population complain of a subjective dry syndrome, only 1% have an 'objective' sicca syndrome, and ultimately only 0.1% have SD.

Finally, it is important to remember that SD may initially present as systemic involvement: peripheral neuropathy, purpura, polyarthritis, myositis, bronchitis, pneumopathy. In some of these patients, dryness may be moderate and should be investigated through patient interviewing.

5.4. Confirmation of diagnosis/differential diagnosis

When faced with a sicca syndrome, seeking a differential diagnosis (Table 2) is as important as seeking positive diagnostic criteria for the disease.

In case of abnormal fatigue, polyalgia or signs of systemic disease (multiple visceral pathology), SD must be suggested and therefore the question of the existence of dryness must be asked, bearing in mind that many polyalergic or fatigued patients have treatments that cause dryness and may even complain of dryness in the absence of a treatment that causes dryness. Thus, the triad of dryness, joint pain, and fatigue that characterises SD is also seen in diffuse polyalergic or idiopathic fibromyalgic syndromes and this will be the most important differential diagnosis.

Swelling of the salivary glands (parotid or submandibular glands), which is rarer, should be considered as soon as it is bilateral or associated with other signs, although the main differential diagnoses should be sought (Table 3).

Table 2
Causes of dry eyes or dry mouth other than Sjögren's syndrome.

Medicines	General risk factors
Strong action	Predisposition
Atropine	Age
Atropinics	Female sex (perimenopause and menopause)
Tricyclic antidepressants (imipramine)	Androgen or ovarian deficiency
Neuroleptics	Chronic diseases
Antiparkinsonians	Poorly controlled diabetes
Morphine analgesics	Dehydration
Weak opioid analgesics	Psychological disorders
Botulinum toxin type A	Graft versus host disease
Class 1A anti-arrhythmics	Dysthyroidism
Anti-histamines, anti-cholinergics	Hepatitis C
Anti-acne drugs (isotretinoin)	Sarcoidosis
Addictive substances (tobacco, ecstasy, cannabis, cocaine)	Amyloidosis
Some chemotherapies	IgG4-associated disease
Moderate action	Depressive syndrome
Beta-blockers	Lifestyle habits
Alpha blockers	Computers or other screens, television, prolonged reading
Calcium inhibitors	Tobacco, alcohol
Benzodiazepines	
Serotonin reuptake inhibitors (antidepressants)	
Local irradiation	Local causes
Head and neck > 30 Grays	Ocular damage
Recovery in 6 to 12 months sometimes	Refractive surgery (laser)
	Blepharitis, Meibomian gland dysfunction
	Nerve damage to the cornea
	Contact lenses
	Mouth diseases
	Craniofacial surgery
	Oral thrush
	Lichen

Table 3
Differential diagnosis of parotidomegaly (after excluding other causes of regional swelling, including adenopathy, masseter swelling, lipoma, cyst).

ENT causes	General illness
Acute parotitis	Exogenous
Lithiasis	Alcohol
Viral: mumps, coxsackie, cytomegalovirus	Undernutrition
Suppurated: streptococcus A or B promoted by age, dehydration, diabetes, alcohol, poor oral condition	HIV
Chronic parotitis	General illnesses
Lithiasis (especially under the jawbone)	Sarcoidosis
Sialodochitis	IgG4-associated disease (formerly called Mikulicz syndrome)
Tumours	Granulomatosis with polyangiitis, formerly called Wegener's disease
Benign: adenoma, myoepithelioma, epidermoid cyst	MALT lymphoma
Malignant: carcinoma, metastasis	Hypothyroidism
	Cushing's syndrome
	Gout
	Diabetes
	Alcoholic cirrhosis
	Nutritional parotidomegaly (anorexia, bulimia, induced vomiting, excessive bread consumption)

HIV: human immunodeficiency virus.

In the absence of a diagnosis that clearly explains the dryness, fatigue, pain, parotidomegaly or visceral involvement, the diagnosis should be made. The ACR/EULAR 2016 criteria will help to guide the diagnosis but other signs not included in these criteria may be helpful in difficult cases. Therefore, the initial diagnostic work-up should include:

- a complete clinical examination, including detailed questioning about functional signs, including respiratory signs (dyspnoea, cough);

- unstimulated whole saliva flow: in the morning, the patients spit every minute for 5 or 15 minutes into a saliva collection device or tube which is weighed, empty and filled, with an analytical balance (the volume is determined according to the formula: 1 mg = 1 mL, the result is expressed in mL/min, normal if > 0.1 mL/min) The collection of saliva can also be done in a 20 mL graduated syringe with collection of saliva for 15 minutes (normal if higher than 1.5 mL/15 min);

- an ophthalmological examination including:

- Schirmer's test, which consists in placing a 5 mm wide strip of paper graduated from 5 mm to 5 mm in the lower conjunctival cul-de-sac (at the junction of the outer 1/3 and the inner 2/3). The impregnation of the paper is assessed after 5 minutes (normal > 5 mm),

- the Ocular Staining score (OSS) which gives the sum of a score of 0 to 3 for fluorescein staining of the cornea and a score of 0 to 6 for lissamine green staining of the nasal and temporal conjunctiva, and severity scores up to 3 depending on the presence of confluence, central involvement or filaments (the score is considered abnormal if $\geq 5/12$ on at least one side). A schematic of the score is presented in the chapter "Ophthalmological involvement";

- a biopsy of the accessory salivary glands (video available: <https://www.fai2r.org/les-tutos/bgsa/>) obtained after eversion of the lower lip, with local anaesthesia using a fine insulin-type needle, through a 3 to 4 mm long incision, perpendicular to the free edge of the lip, opposite the mandibular canine, without suture but manual compression for 5 to 10 minutes using a compress at the end of the procedure. Two to four salivary glands are removed to obtain a sample of ideally at least 8 mm² on a slide. The anatomopathological reading must be done in terms of focus score (abnormal if there is at least one agglomerate of more than 50 lymphocytes for a glandular surface of 4 mm²) within a preserved glandular architecture. The focus score has replaced the Chisholm score which was pathological in the presence of 1 focus/4 mm² (Chisholm grade 3) or more than 1 focus/4 mm² (Chisholm grade 4);

- a chest computed tomography (CT) scan without injection, low-dose if there are pulmonary signs (dyspnoea); the inclusion of parenchymal impairment of the main salivary glands (parotid and submandibular) detected through ultra-sonography in the ACR/EULAR criteria improves the sensitivity of these criteria;

- a laboratory-based assessment (Table 4): C-reactive protein (CRP), complete blood count (CBC), liver function test, ionogram with calcaemia and phosphorus levels, creatinaemia,

creatine phosphokinase (CPK), alkaline reserve, thyroid-stimulating hormone (TSH), urinary figurative element count, proteinuria and creatinuria on sample, protein electrophoresis and weighted immunoglobulin determination, cryoglobulinaemia, anti-nuclear antibodies and specificity (the autoantibodies most suggestive of SD are anti-Sjögren's disease A and B (anti-SSA/Ro60 and anti-La/SSB), with anti-SSA representing the serological item in the ACR/EULAR criteria), rheumatoid factors, C3 and C4 fraction of complement, and potentially beta-2-microglobulin.

The ACR/EULAR 2016 criteria (Table 1) allow for the diagnosis to be considered in any patient with at least one presenting sign (dryness, visceral involvement) and for whom there is:

- a focus score ≥ 1 on the biopsy of the accessory salivary glands and anti-SSA autoantibodies, OR;
- a focus score ≥ 1 on the biopsy of the accessory salivary glands or anti-SSA/Ro60 autoantibodies, and at least one objective criterion of dryness among OSS, Schirmer and pathological flows;
- outside the ACR/EULAR criteria the diagnosis can be considered if there are typical salivary gland abnormalities on ultrasound in addition to the pathological biopsy of the accessory salivary glands or the presence of anti-SSA/Ro60 antibodies but the opinion of a reference centre will be required.

5.5. Immunological diagnosis

The presence of anti-SSA antibodies is a key element of the diagnosis but is only present in 2/3 of patients. It is important to remember several important points concerning these anti-SSA antibodies, also called anti-Ro60:

- the antibodies that should be considered for the diagnosis of SD are anti-Ro60 and not anti-Ro52. Most immunology laboratories only consider the presence of anti-SSA when it is anti-Ro60 but this should be checked;
- the isolated presence of anti-SSA/Ro52 antibodies without anti-SSA/Ro60 and without anti-La/SSB is not specific to Sjögren's disease. These antibodies, called anti-TRIM21, can be found in healthy subjects or in other autoimmune diseases (inflammatory myopathies, autoimmune liver diseases);
- the presence of anti-SSA/Ro60 antibodies points to two systemic autoimmune diseases: SD and lupus;
- these antibodies are useful for diagnosis but not for follow-up because they remain positive throughout life and their titre does not vary with disease activity. They should not therefore be repeated;
- in case of clinical suspicion, but no identification of anti-nucleus antibodies on HEp2 cells, it is possible to ask the laboratory for a screening of anti-SSA/Ro60 antibodies. Indeed, in rare

cases, it is possible to observe no fluorescence on HEp2 cells despite the presence of anti-SSA/Ro60;

- anti-SSB (or anti-La) antibodies are never present in SD without anti-SSA. They are found in half of patients with anti-SSA. The presence of isolated anti-SSB antibodies is most often the result of a false positive laboratory result (just above the threshold) or can very rarely be seen in other systemic diseases. For this reason, they have been removed from the definition of the disease criteria.

Using the ultrasound criteria currently being validated, the diagnosis can be considered in case of:

- a focus score > 1 on the biopsy of the accessory salivary glands or anti-SSA autoantibodies, and at least one of the following 4 objective criteria for dryness

- pathological OSS,
- pathological Schirmer,
- pathological salivary flow,
- salivary ultrasound showing inhomogeneous parenchyma in at least 2 of the 4 glands analysed.

It should be noted that in case of a low probability of SD and in the absence of anti-SSA, a normal ultrasound scan has an excellent predictive value for ruling out the diagnosis, and could thus help avoid the biopsy of the accessory salivary glands in this group of patients.

5.6. Assessment of severity/extent of disease/testing for comorbidities/prognosis assessment

Patients' complaints are generally centred on fatigue, pain and dryness, which are assessed by 3 visual analogue scales (VAS), the average of which constitutes the EULAR Sjögren's disease patient reported index (ESSPRI). Non-specific quality of life scales, such as the SF36, can be used in addition.

The dentist or oral surgeon searches for oral complications (dental deterioration, oral candidiasis, periodontal disease) and the ophthalmologist searches for ophthalmological complications (corneal and conjunctival lesions, damage to the meibomian glands, disturbance of functional visual acuity) and adjusts the frequency of subsequent follow-up according to the local risks.

Table 4

Initial laboratory work-up.

Initial assessment of Sjögren's
Full clinical examination
With detailed questioning on functional signs, including respiratory signs (dyspnea, cough)
Unstimulated whole salivary flow
Ophthalmological examination
Schirmer
OSS
Biopsy of the accessory salivary glands
CT scan of the chest without injection, low-dose if there are pulmonary signs (dyspnoea)
Parenchymal ultrasound of the main salivary glands if available
Standard laboratory testing
CBC
Blood ionogram
Calcaemia, phosphoraemia
Creatinine levels
Urinary figurative elements count
Proteinuria/creatinuria ratio on sample
Liver function test
CRP
TSH
CPK
B-cell activity
Rheumatoid factors
Antinuclear antibodies (anti-SSA/Ro 60, SSB)
Beta-2-microglobulin
Plasma protein electrophoresis and immunofixation
Weighted Ig assay
Complement C4 and C3
Cryoglobulin
Before pregnancy
Anti-SSA/Ro 60 and Ro 52
Anti-cardiolipin
Anti-beta2GP1
Lupus anticoagulant
Standard laboratory testing
Comorbidities
Lipid profile
Initial differential diagnosis
HBV, HCV, HIV serology and viral replication if positive
IgG4 assay
Conversion enzyme
Other autoimmune disease
Myositis antibodies
Native DNA (lupus)
ACPA (rheumatoid arthritis)
Anti-thyroid antibodies
ANCA
Other organ damage
Amylase and lipase

ACPA: anti-citrullinated protein antibodies; ANCA: anti-neutrophil cytoplasmic antibodies; CBC: complete blood count; CPK: creatinine phosphokinase; CRP: C-reactive protein; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; OSS: Ocular Staining Score; TSH: thyroid-stimulating hormone.

Table 5

Main associated pathologies.

Hashimoto's thyroiditis
Systemic lupus
Systemic scleroderma
Inflammatory myopathies
Rheumatoid arthritis
Primary biliary cholangitis
Autoimmune hepatopathy
Biermer's disease
Myasthenia

The assessment of severity is based on the identification of impairments associated with a poor prognosis. This assessment of the extent of the disease is based primarily on clinical examination data, supplemented by paraclinical examinations and specialised consultations when necessary. The most commonly used validated score to quantify this systemic involvement is the EULAR Sjögren's disease activity index (ESSDAI). This is a standardised and validated systemic disease activity score, which groups systemic disease involvement into 12 broad domains. This score is primarily a research tool, but even if it is not completely exhaustive, it can be used in daily practice to perform a systematic inventory of systemic disease activity.

The clinician must therefore make an inventory of all visceral injuries and separate those that are active from those that are sequelae of past injuries.

The ESSPRI and ESSDAI scores are available at: <https://www.sanoia-fiche-sante.com/sjogren>.

SD may be associated with another condition that should be investigated at least clinically (Table 5). In the majority of cases, this is an autoimmune or inflammatory disease, or a lymphoma.

The risk of lymphoma is therefore increased and certain signs are particularly important in suggesting the risk of developing one in the coming years: purpura, parotidomegaly (especially if persistent or recurrent), splenomegaly, adenopathy, monoclonal gammopathy, lymphopaenia, cryoglobulinaemia or rheumatoid factor and low complement levels.

As with any chronic inflammatory disease, particular attention should be paid to the control of cardiovascular risk, and therefore a cardiovascular risk assessment should be performed.

5.7. Diagnosis disclosure and patient information

Diagnosis disclosure should, if possible, be the subject of a dedicated consultation during which the diagnosis, its consequences and the broad outlines of therapeutic management as well as possible adverse events are explained. This information should be presented according to the patient's level of understanding.

It is essential to explain to the patient that SD is not a contagious or genetic disease, and is therefore not transmissible to family members or descendants. In this consultation, it is important to remember that:

- in the absence of systemic complications (2/3 of patients), life expectancy is the same as that of the general population;
- the disease will almost never result in joint destruction or paralysis leading to motor disability;
- although vision may be blurred by dryness, the disease never progresses to blindness.

The patient should also be informed that this is a rare and currently orphan disease, requiring general clinical, but also ophthalmological, odontological, gynaecological as well as laboratory-based monitoring.

The main signs of flare-ups and what to do in the event of a flare-up should be explained to patients. The contact details of patient associations must be made available. If necessary, psychological support may be offered.

5.8. Genetic counselling

The proportion of genetic predisposition to autoimmune disease susceptibility assessed by disease concordance between monozygotic twins compared to dizygotic twins of the same sex remain low and, therefore, genetic factors do not play a predominant role in determining SD.

First-degree relatives, on the other hand, are more likely to have an autoimmune disease than controls.

5.9. Ophthalmological diagnosis

Dry eye in SD is one of the most disabling symptoms. Around 15% of patients with aqueous deficient dry eye syndrome are reported to have SD, with average damage being more severe than in those without SD.

5.9.1. Pathophysiology of ophthalmological damage

SD is an autoimmune disease causing lymphoid infiltration of the lacrimal glands. It leads to reduced tear flow due to inflammatory destruction of the acini and excretory ducts.

This is also associated with nerve damage. The lacrimal gland, its efferent nerves and the afferent nerves of the conjunctiva and cornea form a functional unit, which produces the watery component of the tear film. The lacrimal reflex depends on the integrity of the nerve endings in the cornea. The density of sensory nerve fibres and their functions are decreased in the patient with SD compared to healthy subjects. Functional impairment of the corneal nerves may reduce the ocular symptoms associated with dry eye syndrome but simultaneously lowers the tear reflex, thereby reducing tear production.

Meibomian gland dysfunction is one of the most common causes of dry syndrome, characterised by chronic obstructions of the terminal ducts associated with qualitative and quantitative changes in glandular secretion. It is frequently associated with SD. To improve the symptoms, patients are advised to “squint” their eyes strongly several times a day to “express” (externalise) the product of these glands and avoid obstruction of their terminal ducts.

The concentration of pro-inflammatory cytokines is increased in both SD and all dry eye syndromes. These are mainly interleukins (IL) 1 and 6, IFN γ and tumour necrosis factor alpha (TNF).



Fig. 1. Schirmer test (I), to be performed without anaesthesia.

SICCA Ocular Staining Score

Right Eye

Staining pattern score:

Lissamine Green (conjunctiva only)		Fluorescein (cornea only)	
Grade	Dots	Grade	Dots
0	0-9	0	0
1	10-32	1	1-5
2	33-100	2	6-30
3	>100	3	>30

Extra points—fluorescein only:
(Mark all that apply and add to fluorescein score)

+1 - patches of confluent staining

+1 - staining in pupillary area

+1 - one or more filaments

Total Ocular Staining score:

Left Eye

Lissamine Green (conjunctiva only)		Fluorescein (cornea only)	
Grade	Dots	Grade	Dots
0	0-9	0	0
1	10-32	1	1-5
2	33-100	2	6-30
3	>100	3	>30

+1 - patches of confluent staining

+1 - staining in pupillary area

+1 - one or more filaments

Total Ocular Staining score:

Fig. 2. Ocular Staining Score (OSS).



Fig. 3. Left: lower superficial keratitis (arrows); centre: staining before tear film break-up; right: dye-free areas appear after a few seconds defining the tear break-up time (arrows).

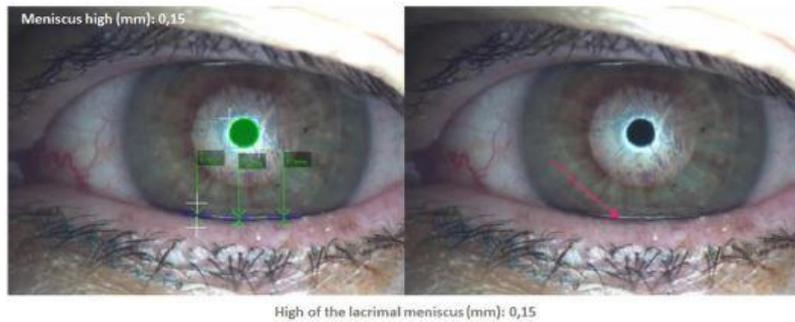


Fig. 4. Assessment of lacrimal meniscus height on photograph – Lacrydiag (Quantel) – This height is measured at three points.

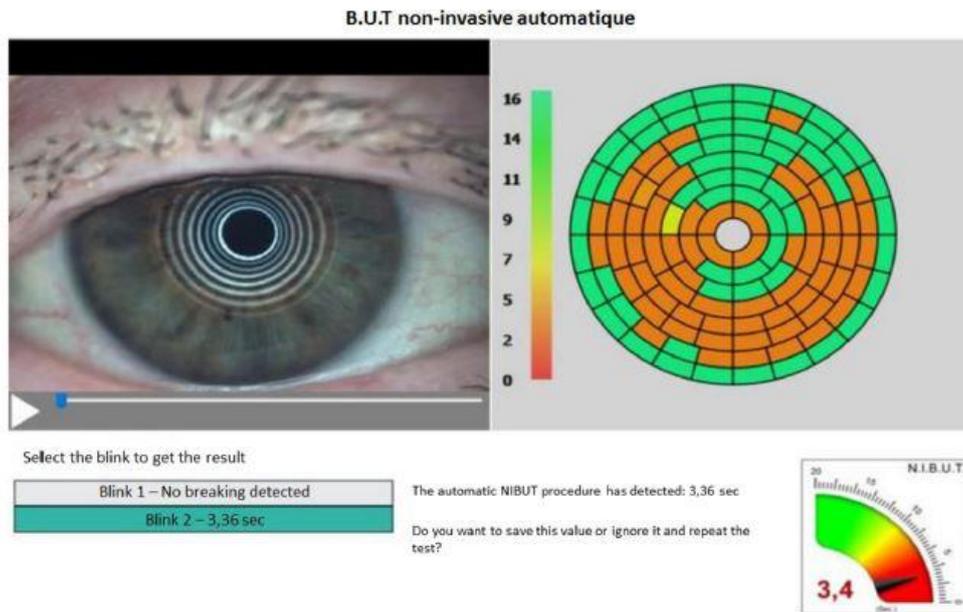


Fig. 5. Evaluation of Non-Invasive Break-Up Time – Lacrydiag (Quantel). On the left, a mire is projected onto the eye. On the right, the time corresponding to the distortion of this test pattern (corresponding to the tear film break-up time) is represented in colour and by sector. In this example, the average time to rupture is 3.36 s.

5.9.2. Functional signs

Dry eyes, gritty feeling, eye pain and itchy eyes are the main symptoms of dry eye in SD.

Multiple quality of life questionnaires have been developed to assess the severity of dry eye disease. The Ocular Surface Disease Index (OSDI) questionnaire is the most widely used. It is easy to understand and assesses three modules through twelve questions: symptoms (sensitivity to light, sensation of grit, pain or irritation, blurred vision and poor vision), discomfort with certain activities (reading, night driving, computer and television) and discomfort related to the environment (wind, low humidity and air-conditioned places).

Other questionnaires such as the Dry Eye Questionnaire (DEQ) or Symptom Assessment in Dry Eye (SANDE), which use analogue scales can also be used.

The dryness symptoms reported by patients remain poorly correlated with glandular damage in SD due to the extent of reduced innervation within the salivary glands and cornea, which also contributes to the lack of saliva and/or tear fluid synthesis.

5.9.3. Anatomical complications

Dry eye in SD may lead to a complication called superficial punctate keratitis, which is a disseminated lesion of the epithelial cell layer of the cornea.

In more severe cases, these lesions can become coalescent and cause real corneal ulcers which can even lead to perforation. Due to the epithelial defect, the risk of infection is increased with possible corneal abscesses.

These disseminated cellular lesions are also present in the conjunctiva and at the free palpebral margin.

SD is also frequently associated with blepharitis with a deficit in the lipid component in addition to the water deficit.

5.9.4. Investigations of the ocular surface

5.9.4.1. Conventional.

The measurement of the aqueous production of the lacrimal gland is assessed by the Schirmer test (Fig. 1). This quantitative test of total lacrimal secretion (basal and reflex) is performed without topical anaesthesia and its result is read 5 minutes after the application of a millimeter blotting paper on the conjunctiva at the junction of the outer 1/3 and inner 2/3. The pathological threshold is 5 mm. However, reproducibility is variable and the association with dry eye symptoms is weak. Do not use artificial tears one hour before the test.

The Van Bijsterfeld score was the first used as a diagnostic criterion. Rose Bengal stains abnormal areas of the cornea and conjunctiva, highlighting areas without mucin. Due to its toxicity, it has now been replaced by lissamine green (for conjunctival staining) and fluorescein (for corneal staining) which are better tolerated dyes. The OSS score (Fig. 2), derived from the Van Bijsterfeld score, adds three criteria of severity: confluence of lesions, central corneal lesions and presence of filaments.

The most recent ACR/EULAR criteria in 2016 are an OSS score ≥ 5 or a Van Bijsterfeld score ≥ 4 in at least one eye and a Schirmer test ≤ 5 mm in 5 minutes.

The tear break-up time (Fig. 3) is an indicator of tear film stability commonly used in the assessment of dry eye syndrome. It is the time it takes for the first dye-free area to appear. The tear break-up time is considered pathological below 5 seconds. It is measured by instilling a drop of fluorescein into the lower conjunctival cul-de-sac and then measuring the time taken for the first tear film break-up area to appear after a blink. The average of three successive measurements is calculated to improve accuracy.

5.9.4.2. More recent ophthalmological tests (under evaluation).

5.9.4.2.1. Lacrimal Meniscus.

The tear meniscus is the concavetear reservoir located at the upper and lower palpebral margins. It is used to assess the aqueous layer of the tear film as an indicator of total tear volume.

Some platforms allow for the assessment of the height of the inferior meniscus from a calibrated photograph (Fig. 4). Anterior segment optical coherence tomography (OCT) allows for an accurate estimation of its volume.

5.9.4.2.2. Non-invasive break-up time (NIBUT).

NIBUT is the time between a blink and the first appearance of a tear film break in the form of distortion or breakage of the tear film patterns (Fig. 5). There are several devices that can evaluate this measure, such as corneal topographers, aberrometers or interferometry. NIBUT is an indicator of the stability of the tear film. The threshold value is currently being validated.

5.9.4.2.3. Imaging of the Meibomian glands.

Meibography allows in vivo examination of the morphology and distribution of the Meibomian glands by means of either transillumination of the everted eyelid with a light source applied to the contact of the eye-lid or without contact by direct infrared illumination (Fig. 6). Some platforms allow automated or semi-automated quantification of the Meibomian gland area.

These tests are not yet used in routine practice in SD. They are not part of the criteria for the classification or diagnosis of the disease but they allow for an overall assessment of the pathological damage and the adjustment of potential treatments for dryness. 5.10. Odontological diagnosis

5.10.1. Physiopathology of oral disease

SD is an autoimmune disease causing lymphoid infiltration of the salivary glands which may result in reduced salivary flow. This hyposialia, which may be mild, moderate or severe, will result in various disabilities depending on the level of salivary gland involvement and the subjectivity of the patient.

5.10.2. Main objectives

The main objectives are:

- to detect and assess hyposialia or asialia, to assess salivary gland involvement;
- to assess the impact on quality of life and functional impact;
- to look for and anticipate possible complications related to hyposialia;
- to make a differential diagnosis with xerostomia or salivary disease of other origin.

5.10.3. Professionals involved

The professionals involved are:

- dental/oral surgeon;
- anatomopathologist;
- imaging (ultrasound).

5.10.4. Diagnosis

It will be essential to look for hyposialia associated with xerostomia.

As a reminder, xerostomia is a subjective sensation characterised by a feeling of dry mouth. It can be present without anyhyposialia being objectified.

The identification of hyposialia is based on questioning (Table 6), clinical and paraclinical examinations.

5.10.5. Interview – History taking

Patient interview is a key element in the diagnostic process.

The presence or absence of risk factors for dental caries such as smoking, alcohol, caffeine consumption and the presence of mouth breathing should be investigated. A potential medical and surgical history (ENT radiotherapy, salivary gland surgery), and medication(anti-cholinergic drugs, opiates, antidepressants, anti-psychotics, diuretics, anti-histamines and antidepressant sympathomimetics, anti-hypertensives, bronchodilators) should also be collected(Table 2).

The duration of the dry mouth sensation should be specified to determine whether it is acute or chronic (> 6 weeks).

The potential impact on daily life should be evaluated because hyposialia is frequently accompanied by a deterioration in quality of life with sensations of burning in the mouth, dysgeusia, dysphagia, changes in eating, and difficulties in speaking. The impact is correlated with the extent of hyposialia.

5.10.6. Clinical examination

The clinical examination by the oral cavity specialist includes a thorough inspection and fine palpation of the oral sphere, i.e. all mucous membranes and periodontal structures, the teeth and finally the salivary glands.

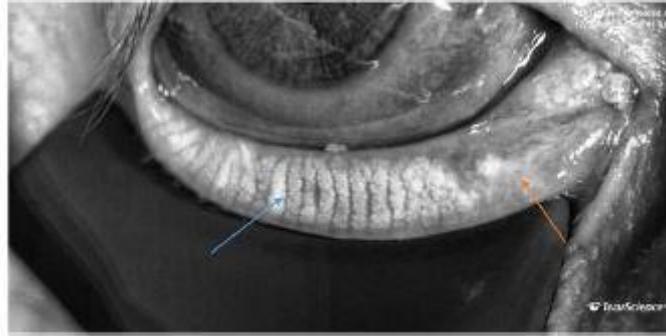


Fig. 6. Infrared imaging of the Meibomian glands for characterisation (including atrophy) – Lipiview (TearScience). The blue arrow represents an area of healthy Meibomian glands. The pink arrow represents an area of atrophy of the Meibomian glands.

Table 6

Recommended interview protocol for suspected hyposialia [43].

1. Do you experience dry mouth at night or when you wake up?
2. Do you experience dry mouth during the day?
3. Do you keep a glass of water beside your bed?
4. Do you take sips of liquid to swallow dry food?
5. Do you experience dry mouth during meals?
6. Do you have problems swallowing certain foods?
7. Do you use chewing gum on a daily basis to eliminate the feeling of dry mouth?
8. Do you eat fruit or suck on hard mints daily to eliminate the feeling of dry mouth?
9. Do you notice a change in your saliva quantity?
10. Do you need to moisten your mouth frequently?

5.10.6.1. Inspection. The quality of the mucosa must be carefully assessed.

It should be analysed whether the mucosa is dry, sticky, shiny or on the contrary well moistened. Moreover, a dry mucosa is more likely to be ulcerated.

Inspection of the tongue will aim to look for lingual atrophy with a smooth, depapilled, fissured, red appearance, or even the presence of crusty deposits in extreme cases of hyposialia.

The periodontal tissues (supporting tissues of the tooth) are thoroughly examined clinically for bleeding, gum swelling or recession, plaque or calculus, or tooth mobility, resulting in a summary document called a periodontal chart (Fig. 7).

In addition, the vast majority of patients with hyposialia have an increased susceptibility to fungal infections (candidiasis), due to the increased presence of *Candida albicans* in these patients and the lower salivary protection of the mucosa.

Patients may experience unpleasant sensations such as burning or stinging on the tongue or mucous membranes, suggesting a diagnosis of secondary stomatodynia.

In terms of dentition, patients with hyposialia are more likely to develop carious lesions preferentially located at the necks of the teeth. This phenomenon is directly linked to the decrease in the flow and changes in the composition of saliva.

In patients with SD, the risk of caries is therefore increased, often despite very good oral hygiene and regular visits to the treating dentist.

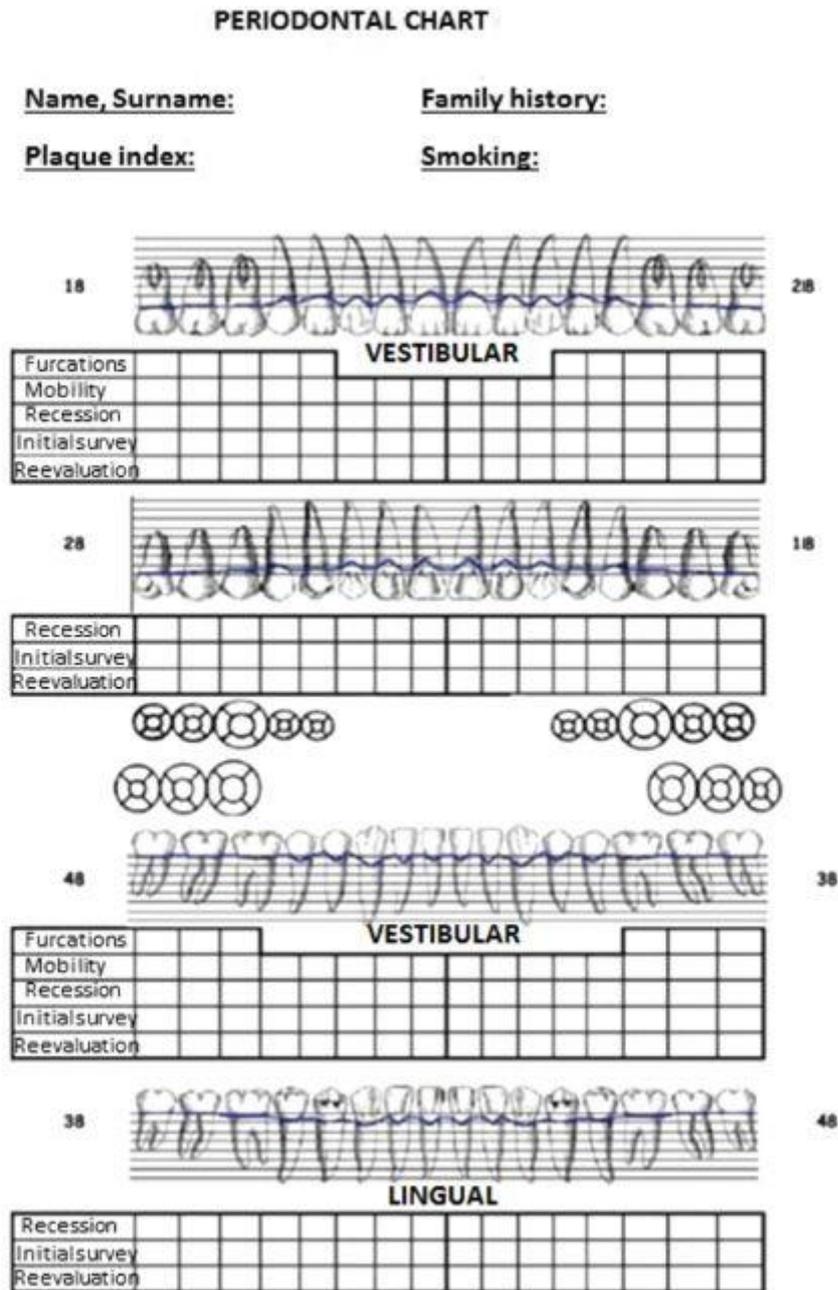


Fig. 7. Periodontal chart.

5.10.6.2. Palpation.

Palpation will allow for the quality of the mucosa to be assessed and thus to see whether it is adherent or not.

It is also necessary to palpate the parotid and submandibular glands in order to stimulate salivary flow and to determine whether or not there is salivary flow at their ostium; the quality of saliva (which is normally fluid but can be frothy or viscous in the case of SD) and its quantity can then be assessed.

5.10.7. Paraclinical testing

Paraclinical testing will make it possible to concretely objectify the decrease in stimulated and/or unstimulated salivary flow and to evaluate the damage to the salivary glands (imaging and histo-anatomo-pathology).

The measurement of salivary flow will allow for an objective differentiation between xerostomia and hyposialia. Two measurements will be performed. First, an unstimulated salivary flow measurement is performed by collecting all the saliva produced by the patient passively (without stimulation) for 5 to 15 minutes. Secondly, a stimulated saliva flow measurement is performed for 5 minutes, with the patient chewing a piece of paraffin, for example, in order to activate the secretion.

Hyposialia will then be characterised by a measurement of the so-called pathological salivary flow when:

- measurement of unstimulated salivary flow is ≤ 0.1 mL/min;
- measurement of stimulated salivary flow is ≤ 0.5 – 0.7 mL/min.

In practice in Sjögren's it is rather the unstimulated salivary flow that is referred to.

The second paraclinical test will consist in performing a biopsy of the accessory salivary glands for histo-anatomopathological purposes to test for chronic sialadenitis. This examination will also allow for a differential diagnosis with amyloidosis, sarcoidosis or IgG4-associated disease.

The final paraclinical test will be an ultrasound of the main salivary glands to study their echo-structure.

5.11. Pathophysiology of skin involvement

Skin involvement may consist of manifestations that can be divided into three categories:

- skin dryness or xerosis;
- manifestations related to the autoimmune context;
- sensory disorders.

Xerosis is by far the most common skin symptom (Fig. 8). It may be related to lymphoid infiltration of the sweat glands, which can even be found in axillary biopsies to help with the general diagnosis of the disease. However, hyposudation may or may not be found depending on the study. This hyposudation may also be related to small fibre neuropathy (SFN) in the most advanced forms. Abnormalities in the expression of aquaporin 5 in the sweat glands could play a role. The sebaceous glands do not seem to be affected. In reality, xerosis is more likely to be related to abnormalities of the epidermal barrier, which are still poorly understood.

The most common manifestations are Raynaud's syndromes, hypergammaglobulinaemic purpura (Fig. 9), manifestations of cryoglobulinaemic vasculitis and erythema annulare (often called subacute lupus) (Fig. 10).

Rarer manifestations are urticarial vasculitis or the cutaneous manifestations of antiphospholipid syndrome. Vitiligo, anetoderma (small atrophic skin lesions), intradermal bullous disease, erythema multiforme and potentially lymphoma are also rare.

Pruritus or related sensations (tingling, pulling, even burning or even skin pain) may be related to xerosis but also to small fibre neuropathies.⁶ Therapeutic management [14, 19, 32, 35, 38–41, 44–92]

6.1. Objectives

Within autoimmune diseases, SD is characterised by a dichotomy of clinical signs:

- the symptomatic triad affecting the majority of patients and impacting their quality of life: glandular manifestations, mainly dry eyes and mouth, pain and fatigue;
- systemic manifestations, affecting about 30–40% of patients, which can lead to irreversible organ damage.

Therapeutic management is therefore focused on these two types of manifestations:

- for the triad of dryness, pain and fatigue, management is most often symptomatic at present, pending the development of effective immunomodulatory molecules;
- while systemic manifestations may justify the use of immunomodulators or immunosuppressants.

The absence of an overall treatment that acts simultaneously on all the manifestations of SD makes therapeutic management particularly individualised. In terms of quality of life, the management of glandular and painful manifestations is primordial. In terms of prognosis, the treatment of systemic damage is the essential objective. It depends on the type and severity of visceral damage.

In the absence of a definitive curative treatment, management therefore sets several objectives, taking into account the time factor:

- in the short-term:
 - improving daily comfort,
 - ensuring optimal management of systemic events,
 - sometimes ensuring functional or even vital salvage in case of severe systemic damage;
- in the medium-term:

- improving and slowing the progression of serious diseases: in particular vasculitis with renal and/or neurological damage, pulmonary damage, and haematological damage,
 - preventing flare-ups of these severe conditions,
 - facilitating conception and motherhood in optimal conditions,
 - preserving quality of life and socio-professional inclusion;
- in the long-term:
- limiting the effects of the disease,
 - limiting the delayed deleterious effects of treatment,
 - monitoring the course of the disease and in particular the risk of non-Hodgkin's malignant lymphoma.

6.2. Professionals involved (and coordination arrangements)

Management is multidisciplinary and coordinated either by the attending physician in conjunction with the specialists and, if necessary, the hospital doctors of the reference and/or competence centre, or directly by the hospital specialist with expertise in SD in case of a severe form of the disease (i.e. with systemic damage), always in conjunction with the attending physician and, if necessary, the hospital doctors of the reference and/or competence centre.

It is carried out by the same professionals as those involved in the initial assessment.

6.3. Therapeutic management (pharmacological and other)

As a preamble, it should be recalled here that the management of patients with SD is marked by a lack of evidence of treatment effectiveness. Thus, treatment decisions are mostly based on the experience of clinicians or on evidence of efficacy of treatments for identical symptoms in other systemic diseases, rather than on scientific evidence of drug efficacy in SD, and treatment choices are based on the assessment of both symptoms and systemic (so-called "extra-glandular") manifestations. Symptomatic treatment is generally appropriate for all patients, while immunomodulatory or immunosuppressive treatment is reserved for systemic complications. With the recent publication of treatment guide-lines by the EULAR Sjögren's Task Torce of the European Society of Rheumatology, a first step towards a more homogeneous and consensual management of SD has been taken. These recommendations are particularly useful for non-specialist health care professionals. Interestingly, these guidelines provide decision trees for the treatment of each of the possible manifestations of SD, whether they are glandular manifestations or systemic complications.

Therapeutic management must be individualised according to the symptoms and disorders presented by the patients. It is based on a multidisciplinary approach:

- for the triad of dryness, pain and fatigue, management is most often symptomatic, based on local or general treatments in the absence of effective immunomodulatory treatments;
- the use of immunomodulators or immunosuppressants should be reserved for systemic manifestations that justify it.



Fig. 8. Xerosis.

We will therefore approach the therapeutic chapter from this angle.

6.3.1. Management of dryness

The therapeutic management of dryness is essentially symptomatic. To date, no immunosuppressive or immunomodulatory background treatment has been shown to be effective in these manifestations, and they are not recommended in this indication. Furthermore, the natural course of glandular dysfunction in SD is, with the exception of the first few years of evolution, relatively stable for long periods of time, with no treatment able to reverse the glandular destruction.

Thus, the chronic course of SD and the relative stability of glandular dysfunction mean that the management of dryness relies on daily and long-term use of therapies. In this context, it is reasonable to recommend the use of therapies with minimal (or at least tolerable and reversible) side effects. Therefore, topical therapies, which provide symptomatic relief and a significant improvement in quality of life without significant side effects, have a rightful place in this context.

6.3.1.1. Dry mouth.

The therapeutic approach to dry mouth should be guided by whether or not there is a persistent ability to produce saliva: this can be assessed by measuring salivary flow with or without stimulation. In the absence of persistent salivary flow, secretagogue treatments are often ineffective.

The following treatments are available for the management of dry mouth (their indications are summarised in Fig. 11).

6.3.1.1.1. Non-pharmacological stimulation.

Non-pharmacological salivary secretion stimulants include gustatory stimulants, such as sugar-free sour candies or xylitol lozenges and/or mechanical stimulants, such as sugar-free chewing gums. Other dietary secretagogues such as lemon or citrus juices are generally poorly tolerated and are deleterious to the teeth already weakened by the disease.

Parotid self-massage can also be offered to patients, both to promote salivation and to drain the often thick residual saliva and reduce episodes of parotid swelling.

6.3.1.1.2. Pharmacological stimulation.

Pharmacological stimulation is mainly based on muscarinic agonists. Two drugs are available worldwide: pilocarpine hydrochloride and cevimeline. In France, only pilocarpine is available. This molecule has shown its effectiveness in a meta-analysis. It provides a significant improvement in dry mouth (measured by a VAS), but with a high frequency of side effects, in particular hyperhidrosis.

To limit these tolerability issues, it is recommended to introduce this treatment in a gradually increasing dose, starting at 2 mg twice a day until a maximum dose of 15 to 20 mg/day in three or four doses. Pilocarpine hydrochloride may also be effective in nasal, bronchial and vaginal dryness. Its effect on dry eyes is more inconsistent (see below).

Oral pilocarpine 2% eye drops could be a substitute for reimbursable compounded capsules, but this use has not been validated (2 drops morning and evening for the first month, then 2 drops morning, noon and evening for the following 2 months, then re-evaluation).

Treatment should be tried over several weeks with gradually increasing doses until a target dose is reached, i.e. the dose that provides decent tolerability and sufficient relief of symptoms. If it is not effective after a few weeks, the treatment should be discontinued.

The most common side effect of pilocarpine is sweating, as all cholinergic neuroexocrine junctions are stimulated. This can be avoided in most cases by gradually increasing the dose. Other rarer side effects are tachycardia and dysuria.

In patients who are intolerant of, or unresponsive to, muscarinic agents, other secretagogues can be offered: these have the advantage of being well-tolerated but their efficacy remains very limited. Some cholagogues such as an etholtrithione or some mucolytics such as bromhexine or N-acetylcysteine are available.

6.3.1.1.3. *Saliva substitutes.*

These substitutes can be offered to all patients to improve dry mouth, especially those with severe salivary dysfunction (lack of residual saliva) and those in whom pharmacological and non-pharmacological means have proved ineffective.

Saliva substitutes are available in the form of gels, sprays and mouth washes. They should ideally have a neutral pH composition; contain fluoride and usually other electrolytes to mimic the composition of natural saliva. Their effectiveness remains very limited in studies. However, they do not have any side effects.

Gel formulations can be poorly tolerated, especially in patients with no residual saliva, due to a sticky feeling caused by their application. Therefore, in this context, many patients prefer to use water to improve their dryness.

6.3.1.1.4. *Preventive measures.*

Initially, the patient should be informed of the substances that can aggravate dry mouth in order to adapt his or her lifestyle (consumption of caffeine, alcohol, tobacco, certain medications [see Table 2]). Acidic food should be limited; if solid foods are difficult to eat, dishes with sauce may be favoured. In addition, hydration throughout the day is recommended (1.5 L/day).

Secondly, the patient should be informed of the possible consequences of dry mouth on the oral sphere, i.e. the increased risk of carious lesions, candidiasis and alteration of the mucous membranes and periodontium, so that he/she can implement daily preventive measures.

Therapeutic education will include the recommendation of twice-daily fluoride brushing, the use of interdental brushes and the proper cleaning of removable prostheses if the patient has any, as well as mouthwashes with sodium bicarbonate.

It is usually recommended to have a dental follow-up every 6 months, which can be adjusted by the dentist according to the patient's oral status.

In case of oropharyngeal candidiasis, local (Fungizone®) or systemic (Triflucan®) antifungals should be prescribed.

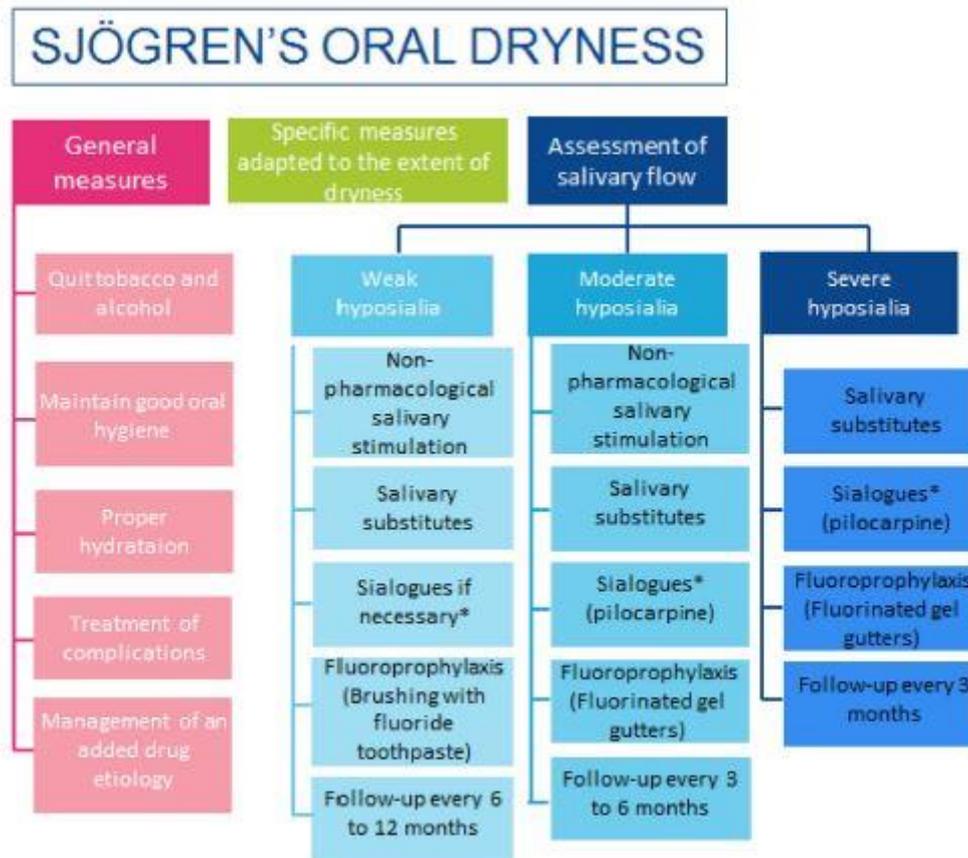


Fig. 11. Decision tree for the management of dry mouth.

6.3.1.1.5. Fluoroprophylaxis.

Fluoroprophylaxis is essential in the prevention of hyposialia-induced caries. In case of mild hyposialia, twice-daily brushing is carried out using a toothpaste with a high fluoride content (e.g. Fluocaril bi-fluoride 250 mg or 2500 ppm®).

In case of moderate to severe hyposialia, an application of fluoride gel with 20,000 ppm of fluoride (Fluogel 2000®) in a tray for 5 minutes daily is recommended in addition to brushing with a fluoride toothpaste. In case of intolerance of the trays, the dental surgeon can carry out a fluoridation at the chair every 3 to 6 months using fluorinated topicals such as

Duraphat® containing 5% of sodium fluoride, i.e. 22600 ppm, or Fluor Protector® containing 1.5% of fluoride, i.e. 7700 ppm.

6.3.1.1.6. Position on implants.

The presence of SD is not a contraindication for implant placement. This treatment is often useful for the quality of life of patients and does not expose them to more side effects than in the general population. Given the importance of this treatment for patients, it would be necessary to have it covered by Social Security.

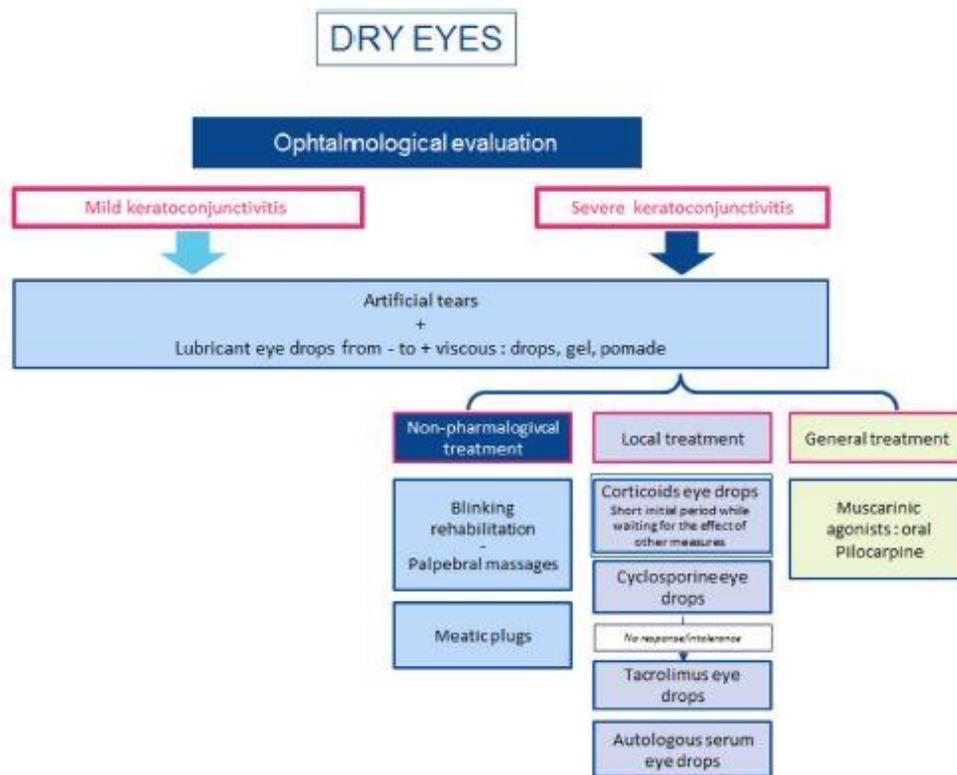


Fig. 12. Decision tree for the management of dry eye. * Pilocarpine is the sialogogue of choice because of its superior and proven efficacy. However, in patients who are intolerant or unresponsive to muscarinic agents, other secretagogues (anetholtrithione or bromhexine or N-acetylcysteine) can be offered. These have the advantage of being well-tolerated but their efficacy remains very limited.

6.3.1.2. Dry eyes.

All patients with SD should have an ophthalmological evaluation to assess the extent of ophthalmic damage. There is no correlation between the severity of perceived dry eye symptoms and the severity of objective ophthalmic damage. The aim is to detect severe forms of keratoconjunctivitis. Different scores are used by ophthalmologists to define the severity of conjunctivitis. For the OSS score, a score ≥ 5 is severe; for the OSDI score, as core ≥ 33 is considered severe; an OXFORD score ≥ 3 is considered severe.

The treatments available for the management of dry eye and their indications are summarised in Fig. 12.

The first line of treatment for dry eye is artificial tears and lubricating eye drops.

Preservative-free eye drops should be preferred, as these are irritating in the event of dry eyes. Artificial tears can be applied as often as necessary to relieve symptoms. It is recommended to combine them with thicker lubricating gels, which have a longer duration of action. These gels mainly contain polymers or viscous agents such as methylcellulose or hyaluronic acid. The advantage of these gels is that they increase the time that the eye drops remain on the ocular surface and therefore have a residual effect to reduce the frequency with which patients need to reapply eye drops. Blurred vision may be observed immediately after application but this gradually fades, and the more rapidly the less viscous the eye drops. These eye drops are usually applied several times a day, but the frequency can be adjusted according to the symptoms.

It is also recommended for all patients to perform regular palpebral massages to avoid obstruction of the Meibomian glands, which produce an oily substance that stabilises the tear film. Indeed, their chronic obstruction is accompanied by their progressive involution and the risk of inflammatory episodes (blepharitis).

6.3.1.2.1. Management of severe keratoconjunctivitis.

Severe keratoconjunctivitis should be managed in an ophthalmic hospital setting with regular follow-up for treatment adjustment.

6.3.1.2.2. Corticosteroid eye drops.

Corticosteroid eye drops can be used for short periods of time, maximum 2 to 4 weeks, due to their risk of side effects, particularly steroid-induced glaucoma. These treatments are generally used in severe forms at the beginning of the treatment in order to reduce inflammation and to be able to introduce ciclosporin eye drops, which can be poorly tolerated when the ocular surface is very inflammatory. These eye drops should be prescribed by specialists.

6.3.1.2.3. Ciclosporin eye drops.

In severe forms of keratorconjunctivitis that do not respond to short courses of corticosteroids, treatment with ciclosporin eye drops is offered. It is offered by hospital pharmacies as a reimbursable magistral preparation for small concentrations (0.05 to 0.1%) and as an ATU (temporary use authorisation) for ciclosporin at 2% (Ciclograft–Kol laboratory). These eye drops are prescribed by specialists. Ikervis is no longer marketed in France.

It should be noted that tacrolimus-based eye drops are beginning to be available in some hospitals specialising in ocular surface diseases and can be offered in cases where ciclosporin eye drops have failed.

6.3.1.2.4. Punctal plugs.

Punctal plugs (often incorrectly called punctal “nails”) are small devices for occluding temporary or permanent tear ducts. Their purpose is to obstruct the tear ducts in order to prevent the tear film from draining and remaining in the eye.

They are fitted by ophthalmologists and very often lead to relief and improvement of symptoms. They are generally well-tolerated. They should be considered as a therapy in their own right in the management of dry eye disease.

6.3.1.2.5. Autologous serum eye drops.

In forms of keratoconjunctivitis refractory to previous therapies, the application of autologous serum eye drops has been proposed with some effectiveness. However, this measure remains a rescue treatment given the difficulties of preparation, the need to keep these eye drops cool and the potential risk of contamination making their shelf life relatively short.

6.3.1.2.6. Protective lenses and scleral lenses.

In the most severe cases, scleral and mini-scleral lenses provide mechanical protection and a tear reservoir. They require a customised adaptation, sometimes long and complex, in a specialised environment.

6.3.1.2.7. Other alternative therapies.

The use of muscarinic agonists, such as pilocarpine, has been evaluated in ophthalmic dryness as well as in mouth dryness. Some studies show a beneficial effect of this treatment. In practice, it seems that this effect is less than what can be observed for dryness of the mouth. The prescription methods and the gradual introduction of pilocarpine remain the same as for dry mouth. Oral anti-oxidant treatments that have been proposed have not proven to be effective.

6.3.1.3. Gynaecological management of vaginal dryness.

SD may manifest as vaginal dryness. This symptom is rarely isolated in the disease, but it may appear very early, or even more rarely, as an entry symptom into the disease. It is often overlooked because it is not always attributed to the disease, but it is insidious and worsens over time, particularly at and after the menopause.

The vulva and vagina are lined with thin, richly innervated and vascularised mucosae. These mucous membranes contain glands and glandular excretory tissues that ensure the lubrication of the vagina and vulva. Thus hydrated, these tissues tolerate rubbing, washing and sexual intercourse. They are under hormonal influence and their good trophicity (suppleness, hydration, tolerance) varies according to cycles and age. Pregnancy, vaginal contraception and radiotherapy can also alter their balance.

In case of a dry syndrome, vulvar and to a lesser extent vaginal tissues may be the site of lymphoid infiltrates found in SD and lose their ability to lubricate.

Vaginal dryness is a general term that can be translated into several types of discomfort:

- inconsistent or sometimes very painful, permanent vulvar itching or pruritus. This leads to scratching lesions, which further aggravate the dryness;
- vulvar burns of varying intensity that occur mainly during contact: when washing, during sexual intercourse or during urination when urine flows over the mucous membranes.;
- dyspareunia: i.e. discomfort and/or pain of varying intensity during sexual intercourse, from the moment of penetration or sometimes only at the end of intercourse. When the dryness is major it can lead to vaginismus, i.e. penetration becomes impossible.

Often latent, these discomforts worsen with the onset of the menopause, as the lack of oestrogen leads to a drop in lubrication.

These symptoms are added to the fatigue directly linked to the disease and to the signs of anxiety and depression that are some-times already present, creating a vicious circle that tends to damage self-confidence and alter romantic relationships. In this respect, it has been shown that they have a very negative impact on quality of life

.6.3.1.3.1. Patient referral.

It is important to discuss the subject with the patient and ideally refer her to a gynaecologist for an appropriate examination. Multidisciplinary teams can refer patients to a gynaecologist who will take the necessary time for the consultation, including all the data on the disease. This approach makes it possible to take into account age, duration of disease, impact on quality of life, sexuality, and current treatment, in order to provide the most personalised response possible.

The dry vulvovaginal syndrome in SD does not increase the risk of genital infection or genital cancers. However, routine screening for cervical cancer is still recommended as for any woman, using the same protocols. It is preferable to carry out this examination with a gynaecologist who will suggest the best way to carry out this screening, taking into account dryness and after appropriate preparation.

6.3.1.3.2. Therapeutic management of vaginal dryness disorders.

Simple hygiene rules:

- it is strongly recommended to stop smoking, which has a negative effect on the blood microcirculation of all mucous membranes;
- avoid “hyper-hygiene” reflexes and the use of irritating products: one or two washes a day are enough, avoid the use of wipes (or water wipes), gels or intimate creams;
- use a gentle cleansing agent or a bar soap that preserves the natural sebum film;
- take the time to rinse carefully and especially to dry with a dry cloth, dabbing without rubbing;

- use cotton or breathable underwear and loose-fitting clothing. If you wear panty liners, choose cotton ones and change them as soon as they get wet;
- avoid sports that irritate the mucous membranes: swimming in a pool, cycling;
- a regular and healthy diet that promotes regular transit is conducive to good colonisation of the anal and therefore vaginal flora.

6.3.1.3.3. Specific treatments.

Depending on the extent of the dryness and the secondary symptoms, which vary from one woman to another, treatments will initially be offered to improve the hydration and tolerability of the vulval and vaginal tissues. The aim is to restore daily comfort and to allow the patient to consider a sex life without fear.

Review of hormonal contraception that is too suppressive for the ovary and increases dryness. SD does not contraindicate the prescription of hormone replacement therapy at menopause, which can improve oestrogenic impregnation and on the contrary reduce or prevent oestrogenic vaginal dryness. An alternative to hormonal treatment of the menopause may be the use of an oestrogenicovum.

Creams or ova with hyaluronic acid or marine collagen, lubricants, based on appropriate and personalised protocols, give good results in regular patients (e.g.: 1 ova of hyaluronic acid/day for 2 weeks then at least 1 ova/week afterwards). Laser vaginal remodelling techniques are being developed and could be a therapeutic option for very severe vaginal dryness.

6.3.2. Pain management

An assessment of the origin of the pain is necessary to adjust pain management. A distinction must be made between two situations: chronic diffuse pain, similar to fibromyalgia, and inflammatory arthralgia. Inflammatory arthralgia as must be managed in the appropriate manner (see the chapter on systemic disorders).

In chronic diffuse pain or fibromyalgia-like presentations that may be associated with a known type of autoimmune SD, there is no need to introduce corticosteroids, HCQ or immunomodulatory therapy. In some cases, these presentations may be due to SFN. The management of pain should be based primarily on non-pharmacological treatments, in particular maintaining appropriate physical activity and cognitive behavioural therapy. Drug management of these diffuse pain syndromes should avoid the use of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and morphine.

Analgesic treatment should preferably be based on level 1 analgesics, giving preference to paracetamol. There is no evidence of superior efficacy of level 2 analgesics (tramadol, codeine, etc.), which can aggravate the dry syndrome and cause dependence or paradoxical hyperalgesia. However, treatments for neuropathic pain such as gabapentin, pregabalin, duloxetine or amitriptyline can be offered, taking into account the benefit/risk ratio and the known risk of aggravation of dryness with these drugs.

6.3.3. Management of systemic disorders

It should be remembered that the forms found in the young subject are often more systemic and severe and therefore justify closer and more prolonged surveillance.

It is important to specify that to date no drug has a marketing authorisation for SD. Thus, all the drugs mentioned in this French NDCP are used outside the MA. Apart from rituximab in cryoglobulinaemic vasculitis, no randomised controlled trial has validated a therapeutic option for the systemic manifestations of SD. However, many trials are being conducted and the data may change rapidly. It is therefore important to seek expert advice when in doubt about the treatment of systemic disease and not to hesitate to suggest that patients be included in ongoing or future therapeutic trials.

The recommendations in the French NDCP are therefore based on expert opinion and retrospective series. As mentioned above, the choice of treatment will be based on a collegial and multi-disciplinary discussion taking into account the type of systemic involvement and its severity. The severity of the disease can be assessed by taking into account the low/moderate/severe grades described in the ESSDAI. The use of reference and/or competence centres to guide the treatment approach strategy in severe or resistant forms is strongly recommended.

6.3.3.1. Therapeutic modalities.

6.3.3.1.1. Place of corticosteroid therapy.

Given its likely long-term toxicity, corticosteroid therapy should not be used as background treatment in SD or as treatment for the polyalgic syndrome. However, it can be initiated during a systemic flare up and in this situation a withdrawal goal should be planned. In the majority of severe cases, the threshold of 5 mg/day of prednisone equivalent 3 months after initiation is reasonable and helps to guide the tapering.

6.3.3.1.2. Conventional immunomodulatory treatments.

Hydroxychloroquine (HCQ). Numerous retrospective and open-label studies have suggested a possible benefit of HCQ in patients with joint pain, or hypergammaglobulinaemic purpura. However, one randomised crossover trial and one randomised double-blind placebo-controlled trial did not show significant improvement in the pain associated with the polyalgic syndrome. There is no evidence to suggest that HCQ improves dryness or fatigue.

Clinical and systemic lupus experience sometimes leads to HCQ being suggested for inflammatory joint pain or polyarthritis.

Finally, controlled studies have shown a decrease in hypergammaglobulinaemia with HCQ. This hypergammaglobulinaemia may be associated with vascular purpura. Thus, HCQ can be offered for this skin complication associated with hypergammaglobulinaemia.

It should be remembered that the use of doses higher than 6.5 mg/kg/day should be avoided over a long period of time and that a determination of hydroxychloroquine levels can be carried out (See CRI-FAI2R sheets).

Methotrexate. This treatment has not been evaluated in a randomised controlled trial. In routine practice, methotrexate is used in patients with inflammatory arthralgia or polyarthritis refractory to HCQ. It is also used in the treatment of myositis.

Leflunomide. Until the publication of a recent randomised clinical trial, the use of leflunomide was restricted to patients with inflammatory arthralgia or polyarthritis refractory to treatment with HCQ and methotrexate (or with contraindications to these treatments). A recent controlled trial of leflunomide plus HCQ, evaluated in a double-blind, placebo-controlled study in 21 patients, showed a significant reduction in ESSDAI scores. The value of leflunomide combined with HCQ needs to be confirmed in a large European trial.

Azathioprine, mycophenolate mofetil. These treatments have not been evaluated in controlled trials in SD. They may be considered as a corticosteroid-sparing treatment for diffuse interstitial lung disease, autoimmune cytopenia, myositis, and mono-neuritis multiplex in the context of vasculitis complicating SD. It should be remembered that mycophenolate mofetil is a teratogenic drug and should therefore be used with caution in women of childbearing age.

Cyclophosphamide. This treatment has not been evaluated in a controlled trial in SD. It is an induction therapy for severe, life-threatening systemic complications (e.g. myelitis, meningoencephalitis, myocarditis, refractory forms of mono-neuritis multiplex, glomerular involvement, or severe diffuse interstitial lung disease), or refractory forms of the disease (cryoglobulinaemic vasculitis refractory to B-cell therapy).

Intravenous immunoglobulins. Apart from rare cases of severe cytopenia, chronic polyradiculoneuritis, very disabling ganglionopathy, or refractory or very severe myositis (swallowing disorders), there is no indication for treating SD with intravenous immunoglobulins. This treatment is being evaluated in axonal sensory neuropathy or SFN (TINISS trial underway, SFN trial to come).

6.3.3.1.3. Targeted therapies.

When using off-label targeted molecules, with the exception of rituximab, it is advisable to include patients in the national observational registry TATA (Targeted Therapies in Autoimmune diseases), whose objective is to evaluate the efficacy and safety of these molecules in autoimmune diseases refractory to conventional treatments.

Anti-TNF therapies. Two placebo-controlled trials have shown the lack of efficacy of anti-TNF drugs, which are therefore not indicated in SD. In addition, BAFF transgenic mice (a cytokine that is increased in SD) have an increased risk of lymphoma occurrence when disabled for TNF or treated with anti-TNF therapy.

B-cell targeted therapies. None of the 4 randomised trials testing rituximab assessed improvement in systemic disease as a primary endpoint. The 2 trials that did assess it as a secondary endpoint did not show significant improvement. However, these trials mainly included patients with moderate or no systemic involvement. Retrospective and registry data suggest the value of rituximab in cryoglobulinaemic vasculitis, autoimmune cytopenia, myelitis, some types of myositis, some types of interstitial nephropathy, and some types of diffuse interstitial lung disease.

In 2021, given the efficacy of rituximab in cryoglobulinaemic vasculitis in general (in both SD-related and non-SS-related forms, see French NDCP cryoglobulinaemic vasculitis), and the pathogenic role of the B-cell in cryoglobulinaemia, rituximab is the first-line treatment for cryoglobulinaemic vasculitis complicating SD. However, patients should be warned of a possible increased risk of serum disease due to anti-rituximab immunisation that is more common in systemic autoimmune diseases than in rheumatoid arthritis.

As blocking the B-cell pathway in general remains a target in SD (in relation to its pathophysiology), other anti-B-cell therapies are being discussed: belimumab, an anti-BAFF monoclonal antibody, or Obinutuzumab, an anti-CD20 antibody more depleting than rituximab. They can be offered in case of intolerance, immunisation or ineffectiveness of rituximab (and with inclusion in the TATA registry). With regard to belimumab, in systemic complications of SD other than cryoglobulinaemia, it has only been evaluated in one trial and more recently in a controlled trial evaluating the value of the combination of rituximab and belimumab and belimumab alone. The results presented at EULAR 2021 show encouraging results for rituximab/belimumab or belimumab alone. However, to date, belimumab should be prescribed mainly in clinical trials (ongoing trial in cryoglobulinaemic vasculitis), or reserved for certain refractory systemic forms, after advice from a reference centre (with inclusion in the TATA registry).

Ianalumab, a monoclonal antibody targeting the BAFF receptor (not available at the time of writing), which also has a B-cell depletion effect, showed a significant decrease in ESSDAI in a phase II randomised clinical trial versus placebo, which needs to be confirmed in a phase III trial.

Iscalimab, a monoclonal antibody targeting CD40 (not available at the time of writing), which inhibits CD40-mediated B-cell activation, showed a significant reduction in ESSDAI in a phase II randomised clinical trial versus placebo, which needs to be confirmed in a phase III trial. Other treatments targeting either CD40 or CD40L are under evaluation.

The updating of the vaccination schedule and the recommended vaccinations while on immunosuppressive drugs (influenza, pneumococcus, COVID-19) must be anticipated before the start of treatment, because of the negative impact on the vaccination response.

Anakinra. The effect of interleukin-1 (IL-1) beta inhibition on systemic activity has not been evaluated in a clinical trial (one clinical trial, including 26 patients, evaluated its effect on fatigue which was negative). There is therefore no indication to treat patients with SD with anakinra.

Abatacept. Two controlled trials showed no efficacy of CTLA4-Ig, a T cell co-stimulation inhibitor, on systemic disease complications. However, a decrease in signs of disease activity measured through laboratory testing such as IgG and rheumatoid factor levels was shown and a re-analysis of these trials with a different endpoint (CRESS) shows a possible benefit. However, these results are insufficient to propose treatment with abatacept in SD, except in certain systemic forms refractory to anti-B-cell therapy and after advice from a reference centre (with inclusion in the TATA registry).

Tocilizumab. A recent controlled trial has shown the lack of efficacy of IL-6 receptor inhibition on the systemic complications of the disease. Therefore, there is no indication to treat patients with SD with tocilizumab.

Anti-IL12/23, anti-IL17. No controlled trials have evaluated the effect of anti-IL-12/23 or anti-IL-17 in SD. There is therefore no indication to treat patients with SD with these targeted therapies.

Kinase inhibitors. Numerous trials are under way to assess the value of JAK/STAT or BTK inhibitors. Apart from clinical trials and particularly refractory systemic complications (inclusion in the TATA registry), there is currently no indication for treatment with kinase inhibitors apart from nintedanib, which is a triple anti-tyrosine kinase targeting PDGFR, VEGFR and FGFR, which is an anti-fibrotic agent discussed in the chapter below

.6.3.3.1.4. Other treatments.

Anti-fibrotic therapies for the treatment of interstitial lung disease. At the time of writing, two anti-fibrotic drugs, pirfenidone and nintedanib are approved for the treatment of idiopathic pulmonary fibrosis. Nintedanib showed a significant but very moderate reduction in functional decline (forced vital capacity, FVC) in progressive fibrosing lung disease outside of idiopathic pulmonary fibrosis including patients with connective tissue disease. Disease progression was characterised by the combination of a decrease in FVC, worsening of symptoms, or worsening of CT signs of fibrosis within the previous 24 months. This clinical trial mainly included patients with rheumatoid arthritis or systemic scleroderma. A smaller German study also showed the benefit of pirfenidone in progressive fibrosis lung disease. As the pathophysiology of interstitial lung disease in scleroderma shares some commonalities with SD, and pending specific data for SD, the indication for this type of treatment, either alone or in combination with immunomodulatory therapy, may be discussed with expert pulmonologists at centres of reference and centres of competence for rare diseases in case of progression of interstitial lung disease. The collection of data on the efficacy and tolerability of the treatment in the TATA registry is useful.

6.3.3.2. Treatment of the different manifestations. See Table 7.

6.3.3.2.1. Joint manifestations.

In case of inflammatory arthralgia, NSAIDs can be offered as an option in the absence of contraindication. In the event of an insufficient response, back-ground treatment with HCQ may be initiated at a dosage of 400 mg/day, not exceeding 6.5 mg/kg. This recommendation is

based on expert opinion. There are no controlled studies evaluating HCQ specifically for joint involvement in SD. As mentioned above, there is one negative trial evaluating HCQ in SD, but the primary endpoint of this trial was improvement in symptoms of pain, fatigue and dryness.

If synovitis is present, NSAIDs can be used for symptomatic purposes. If this fails, low-dose corticosteroid therapy (0.3 mg/kg/day) can be initiated with the aim of rapid withdrawal. In all cases, it is legitimate to associate a background treatment from the outset:

- HCQ in 1st line;
- if unsuccessful: methotrexate at the dosage indicated for rheumatoid arthritis and leflunomide if intolerant;
- in case of resistance to these first two lines, treatment with a bio-logic DMARD may be discussed. Rituximab is the treatment for which there is a relative consensus among experts: despite the lack of evidence of efficacy in the literature, there is data in favour of its efficacy in joint disease. This data comes from registries, notably the French Auto Immunity and Rituximab (AIR) registry, and from retrospective series. Again, no controlled study has demonstrated the efficacy of this treatment in SD. The proposed dosing regimen is that for rheumatoid arthritis, i.e. 1000 mg on days 1 to 15.

6.3.3.2.2. Glandular manifestations.

In case of swelling of the salivary glands, corticosteroid therapy of 0.3 to 0.5 mg/kg/day for 3 to 5 days can be offered in combination with symptomatic measures such as parotid massages. The massages should then be continued over the long-term to avoid recurrence. It is important to look for signs of superinfection, which would justify a combined antibiotic therapy. In case of severe and recurrent or persistent disease, treatment with rituximab may be discussed after consulting the reference/competence centres, after careful evaluation of the benefit/risk ratio and after ruling out lymphoma.

6.3.3.2.3. Cryoglobulinaemic vasculitis.

With the arrival of the curative treatment of hepatitis C, SD has become the 1st cause of mixed cryoglobulinaemic vasculitis. Rituximab is the first-line treatment in combination with bolus corticosteroids in severe forms.

The choice of administration schedule for rituximab is subject to debate. Indeed, a risk of post-infusion worsening has been described with high doses of rituximab. The mechanism involved is not clearly established. Various hypotheses have been suggested: release of cryoglobulin by apoptosis of B lymphocytes or activation of the latter, formation of rituximab/CD20 immune complexes recognised by cryoglobulin and promoting its precipitation. Factors associated with this complication are underlying renal or B-cell disease and high cryoglobulin levels. Thus, the rituximab regimen is not an identified factor, but given the mechanistic assumptions, the hemopathy-type regimen (375 mg/m² weekly, 4

consecutive weeks) rather than a 1000 mg regimen on D1 and D15 may be discussed in patients with any of the 3 risk factors listed above.

Table 7
Treatment of the different manifestations of Sjögren's disease.

Organ and type of damage	First-line treatment	Second-line treatment	Third-line treatment
Glandular Outbreak of glandular swelling, parotitis	Corticosteroid therapy 0.3 to 0.5 mg/kg/day for 3 to 5 days + parotid massage	To be discussed with reference/competence centre; rituximab in severe forms	
Joint Inflammatory arthralgias Polyarthritits	NSAIDs for a short period HCQ 400 mg ± NSAIDs or corticosteroids (<0.3 mg/kg) then rapid withdrawal 6–12 weeks	HCQ 400 mg/day Methotrexate 15 to 25 mg/week If failed or intolerant: leflunomide 20 mg/day	Rituximab 1 g D1–D15
Active cryoglobulinaemic vasculitis	Rituximab 375 mg/m ² × 4 or 1000 mg × 2 ± corticosteroid bolus if severe	To be discussed with reference/competence centre; rituximab + belimumab	To be discussed with reference/competence centre; cyclophosphamide
Severe neurological, skin or membranoproliferative glomerulonephritis	Rituximab (choice of dosing regimen) Favour 375 mg/m ² /week × 4 for the first treatment if renal impairment or lymphoma or high cryoglobulin level No systematic retreatment (retreatment on clinical relapse)	Alternatives to be discussed with reference/competence centre: – severe/anti-B-cell refractory forms: cyclophosphamide or plasma exchange, Belimumab–rituximab combination – cases of immunisation to rituximab – other anti-B-cell treatment	
Skin Cutaneous lupus	Topical corticosteroids, if unsuccessful topical tacrolimus then low-dose systemic corticosteroids (<0.3 mg/kg/day, <4 weeks)	HCQ 400 mg/day	
Hypergammaglobulinaemic purpura	HCQ 400 mg ± low-dose systemic corticosteroid therapy (<0.2 mg/kg/day, <4 weeks)	To be discussed with reference/competence centre; rituximab in severe forms	
Pulmonary Bronchial disease	No immunosuppressive therapy. Inhaled therapies	To be discussed in case of bronchiectasis with frequent superinfections or severe bronchiolitis; treatment with macrolides for anti-inflammatory purposes	
Progressive diffuse interstitial lung disease	Corticosteroid therapy (0.5 mg/kg/day) with rapid reduction (5 to 10 mg at 3 months) + mycophenolate mofetil or azathioprine	Alternatives to be discussed according to the inflammatory component and the phenotype of progressive pulmonary fibrosis with a reference/competence centre: cyclophosphamide or rituximab ± anti-fibrotic agent (nintedanib, pirfenidone) Rituximab for lymphoid interstitial lung disease	To be discussed with reference/competence centre; combination with an anti-fibrotic agent
Organizing pneumonia	Corticosteroid therapy (0.5 mg/kg/day) with rapid reduction for discontinuation within 3–6 months		
Lymphoid interstitial pneumonia			
Renal Tubulointerstitial nephropathy with renal failure	Corticosteroids (0.5 to 1 mg/kg/day, depending on severity), tapered over 6 months depending on clinical response See cryoglobulinaemic vasculitis	To be discussed with reference/competence centre; immunosuppressant: rituximab, mycophenolate mofetil, azathioprine	
Membranoproliferative glomerulonephritis of cryoglobulinaemia			
Muscular Myositis	Methotrexate 20 to 30 mg/week ± corticosteroids (0.5 to 1 mg/kg depending on severity, decrease over 3 to 6 months)	Rituximab or mycophenolate mofetil or azathioprine	Intravenous immunoglobulins
Peripheral nervous system Pure sensory neuropathy, SFN	No immunosuppressive treatment Symptomatic treatment in the absence of progression See cryoglobulinaemic vasculitis		
Cryoglobulinaemia-related multiple mononeuropathy or axonal sensory-motor neuropathy			
Chronic inflammatory demyelinating polyradiculoneuritis	Monthly intravenous immunoglobulins (2 g/kg; over 3/4 days)		
Ganglionopathies	No immunomodulatory treatment	To be discussed with reference/competence centre; rituximab or intravenous immunoglobulins or mycophenolate mofetil or cyclophosphamide	
Central nervous system Myelitis or vasculitis	Cyclophosphamide + corticosteroids (bolus and then 0.5 to 1 mg/kg depending on severity) decrease over 3 to 6 months Rituximab + corticosteroids (bolus)	Rituximab or cyclophosphamide	
Neuromyelitis optica		Plasma exchange	
Haematological Autoimmune thrombocytopenia (<30,000/mm ³ or bleeding)	Corticosteroid therapy (0.5 to 1 mg/kg, depending on severity) decrease over 1 month ± if bleeding: intravenous immunoglobulins (1 g/kg D1 and D2) one course	Rituximab 375 mg/m ² /week × 4	
Autoimmune haemolytic anaemia	Corticosteroid therapy (0.5 to 1 mg/kg, depending on severity) reduction over 3 months	Rituximab 375 mg/m ² /week × 4	
MALT lymphoma	To be discussed in multidisciplinary meeting: – rituximab + alkylating agent (chlorambucil or bendamustine) – or rituximab + fludarabine purine analogue		

HCQ: hydroxychloroquine; MALT: mucosa-associated lymphoid tissue; NSAIDs: non-steroidal anti-inflammatory drugs; NSIP: non-specific interstitial pneumonia; UIP: usual interstitial pneumonia.
*Comprehensive management of respiratory symptoms will include preventive measures such as vaccinations, exercise rehabilitation, respiratory physiotherapy and potential contact with a lung transplant team.

Rituximab treatment can achieve remissions that are some-times very prolonged, so systematic retreatment is not offered, but retreatment only when clinical signs reappear.

In case of refractory or rapidly relapsing forms after rituximab, the combination of rituximab and belimumab has been reported (therapeutic trial in progress). In the most severe forms, particularly in cases of severe renal damage with rapidly progressive glomerulonephritis, plasma exchange and cyclophosphamide may also be considered.

Finally, in patients who initially responded to rituximab but are immune to it, other anti-B-cell therapies (obinutuzumab) may be offered, after discussion with a reference or competence centre.

In case of associated lymphoma, chemotherapy with rituximab may be indicated (see section on lymphoma)

.6.3.3.2.4. Skin manifestations.

Xerosis of the skin is a common manifestation of SD but is not a systemic condition. Treatment is based on emollients. The systemic skin manifestations of SD are diverse, the most common being erythema annulare and purpura, indicative of leukocytoclastic cutaneous vasculitis.

Raynaud's syndrome, when it becomes disabling, requires symptomatic treatment (protection against the cold, calcium channel blockers, etc.).

As indicated in the EULAR guidelines, in case of limited erythema annulare or cutaneous lupus lesions, treatment with topical corticosteroids may be offered as first-line therapy followed by treatment with 0.1% topical tacrolimus (off-label). In the event of non-response or diffuse involvement, low-dose systemic corticosteroids (< 0.2 mg/kg/day) combined with background treatment with HCQ may be offered and in the event of failure, treatment with thalidomide under compassionate use may be discussed. This proposal is based on expert opinion and data from the literature on cutaneous lupus.

The onset of purpura should be investigated for cryoglobulinaemic vasculitis and treatment should follow the recommendations given above. In case of limited purpura without cryoglobulinaemia, a short course of corticosteroids may be suggested. Based on clinical cases and expert opinion, HCQ can be used as background treatment in moderate purpura, especially in the presence of hypergammaglobulinaemia. Compression stockings are helpful ***when purpura is influenced by orthostatism.***

6.3.3.2.5. Muscle damage.

In the event of objective inflammatory muscle damage, i.e. with elevated CPK, electromyogram or magnetic resonance imaging (MRI) abnormalities, inclusion myositis should be ruled out, as the association with SD is preferred. If this diagnosis is ruled out, oral corticosteroid therapy combined with methotrexate should be offered. If this fails, background treatment with azathioprine or mycophenolate mofetil or rituximab may be offered.

Intravenous immunoglobulins may be offered in severe or refractory forms, usually temporarily while waiting for the effect of background treatments.

6.3.3.2.6. Renal manifestations.

Renal involvement in SD is particularly heterogeneous and management depends on the type of involvement and its severity. By far the most common form of renal involvement is tubule-interstitial nephropathy, which accounts for almost 75% of renal involvement in SD. It may manifest itself as ionic disturbances without a clear alteration of the glomerular filtration rate (GFR) including: hyperchloremic metabolic acidosis, hypokalaemia, hypercalciuria (with the risk of lithiasis and nephrocalcinosis) or more often as progressive renal failure with low rate tubular proteinuria. Glomerular disorders are much rarer, mainly membranoproliferative glomerulonephritis, most often associated with cryoglobulinaemic vasculitis (see dedicated section). In mild cases of tubule-interstitial nephropathy, i.e. without a drop in GFR, only symptomatic measures can be offered, mainly the correction of metabolic disorders with potassium supplementation and correction of acidosis (with potassium chloride and sodium bicarbonate) in case of mild disorders. In case of complete distal tubular acidosis with hypercalciuria, hypocitraturia and lithiasis, a specialised investigation is necessary with more specific treatment such as potassium citrate (usually magistral preparations, to be handled with caution in case of renal insufficiency) and hypocitraturia in case of lithiasis. In these cases, renal interstitial inflammation may be absent or minimal (symptoms related to an antibody directed against tubular transporters) and may not warrant investigation and/or corticosteroid therapy. However, early tubule-interstitial nephropathy with tubule-interstitial infiltration and tubulitis should not be overlooked and would require renal biopsy and corticosteroid therapy. It is therefore necessary in these patients with tubule-interstitial nephropathy to monitor GFR and ionic disorders at least 2 to 3 times a year. Even in cases of isolated ionic disorders, it is preferable to request nephrological follow-up: indeed, end-stage renal failure, although rare and progressive, is still possible during tubule-interstitial nephropathy.

In tubule-interstitial nephropathy with moderate to severe involvement, i.e. with the onset of renal failure, a renal biopsy is essential to establish the tubule-interstitial nephropathy, its intensity and the type of lymphocytic infiltration. Systemic corticosteroid therapy is offered (0.5 to 1 mg/kg/day). To date, the value of adding an immunosuppressive treatment at the outset has not been demonstrated, but is recommended as a corticosteroid-sparing measure. This combined immunosuppressive treatment will be either rituximab, mycophenolate mofetil or azathioprine and the choice may be guided by the majority type of lymphocytic infiltrate (B or T). In case of refractory forms (steroid-resistant or dependent), the choice of 2nd line should be discussed in the multidisciplinary meeting within the reference/competence centres.

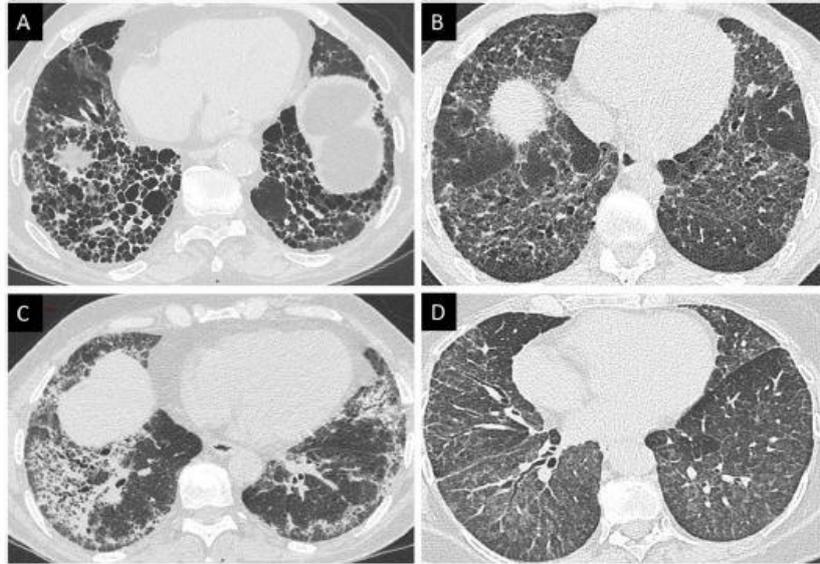


Fig. 13. Computed tomography findings in patients with Sjögren's disease (SD). A. Honeycombing images in both lower lobes showing usual interstitial pneumonia. B. Appearance of fibrosing non-specific interstitial pneumonia. C. Combination of reticulations, ground glass and consolidations suggestive of non-specific interstitial pneumonia with organizing pneumonia. D. Reticulations with ground glass and thickening of the interlobular septa histologically consistent with lymphoid interstitial pneumonia.

In case of membrano-proliferative glomerulonephritis, treatment is based on corticosteroid boluses combined with immuno-suppressive treatment (rituximab, cyclophosphamide). Plasma exchange may be offered in severe or refractory forms.

6.3.3.2.7. Bronchopulmonary manifestations.

Again, SD is characterised by its great heterogeneity. It should be remembered that an isolated cough is not a systemic pulmonary manifestation but is often associated with bronchial mucosal inflammation, which is very common. Respiratory involvement must therefore be demonstrated by pulmonary function testing (PFT) and thin section chest CT scan (Fig. 13).

Bronchial and bronchiolar involvement complicating SD maybe objectified by obstructive ventilatory disorder and images of bronchial dilatation, air trapping and mosaic appearance. Centro-lobular micronodules may indicate cellular bronchiolitis. A corticosteroid test may be suggested for cellular bronchiolitis. For bronchial diseases, immunosuppressive drugs are ineffective or even deleterious, as they increase the risk of infectious complications. Only symptomatic treatment with bronchodilators (possibly combined with inhaled corticosteroids) is then recommended. In case of repeated superinfections linked to bronchiectasis, treatment with low-dose macrolides (erythromycin 500 mg/day or azithromycin, 250 to 500 mg/day, 3×/week) with both anti-inflammatory and anti-infectious aims can be offered. Rare forms of bronchiolitis improving with immunosuppressive treatment have been described and may require a treatment discussion with a reference or competence centre.

The coexistence of parenchymal and bronchial involvement is frequently reported in SD.

A particular feature of SD is the relatively common presence of thin-walled cystic images (Fig. 14). CT scan may show several basic lesions, predominantly in the lung bases: diffuse ground glass, condensations, reticulations, nodules and cystic images. The level of correlation between CT scan and histology is generally quite good. The most common expression of non-specific interstitial lung disease is the combination of ground glass and reticulations, predominantly basal. Bronchiectasis is usually proximal and spares the extreme periphery of the lung, whereas in common interstitial lung disease it is more often subpleural, with a basal, bilateral, peripheral distribution of reticulations, bronchiectasis and a honey comb pattern, sometimes described as exuberant and in the four corners of the lung (four corners sign).

The interstitial lung diseases (ILD) encountered, in decreasing order of frequency, are: non-specific interstitial pneumonia (NSIP), organising pneumonia (OP), usual interstitial pneumonia (UIP), lymphoid interstitial pneumonia (LIP), pulmonary lymphoma of the MALT type, amyloidosis and rarely pleuroparenchymal fibroelastosis. In addition to characterising the type of disease, it is essential to be able to determine its evolution in order to make an appropriate therapeutic decision.

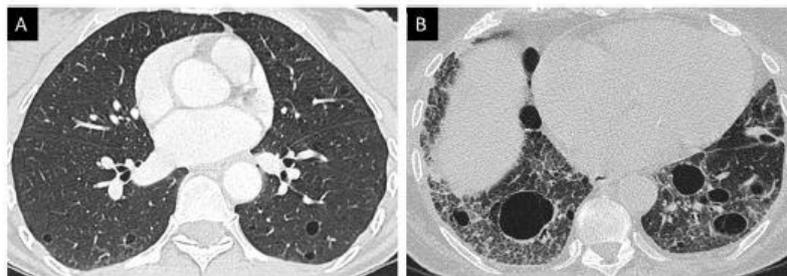


Fig. 14. A. A few well-limited cysts detected on a computed tomography (CT) scan for dyspnoea assessment in a patient with Sjögren's disease (SD). B. Extensive cystic lesions causing respiratory failure.

Box 1: Criteria for progression (or worsening) of interstitial lung disease used in INBUILD [93,94]

In the 24 months prior to the assessment, one of these criteria was relevant to progression:

- relative decline $\geq 10\%$ in FVC expressed as % of predicted value (e.g. FVC declines from 70% to 63% of predicted value);
- relative decline of 5–10% in FVC as % of predicted value and increased symptoms;
- relative decline of 5–10% in FVC as % of predicted value and worsening on scan;
- increased symptoms and worsening on scan;
- some experts [2] suggest that the following criterion should also be used:
 - relative decline between 5 and 10% of FVC as % of predicted value and relative decline $\geq 10\%$ of DLCO as % of predicted value.

OP, NSIP and LIP are usually corticosteroid-sensitive. LIP diagnosed on the basis of a suggestive appearance with ground glass and cysts with lymphocytic alveolitis on bronchoalveolar lavage or OP with alveolar condensation require histological confirmation,

especially if they are refractory to corticosteroids, so as not to overlook a lymphomatous complication or amyloidosis.

In case of severe (with PFT impairment) or progressive NSIP (see Box 1), test corticosteroid therapy at a dosage of 0.5 mg/kg/day with rapid reduction (goal: 5 mg at 3 months) may be offered with re-evaluation at 3 months. In the most severe forms or for the purpose of corticosteroid-sparing, the addition of an immunosuppressive treatment may be offered. Mycophenolate mofetil or azathioprine is offered in 1st line. If this fails, treatment with rituximab or cyclophosphamide may be considered.

In UIP, improvement is not expected with corticosteroid therapy but an immunosuppressive treatment can be discussed on a case-by-case basis to avoid worsening. Nintedanib (an anti-fibrotic molecule) now has a marketing authorisation for the treatment of progressive fibrosing ILD, including fibrosing ILD associated with SD. There is also data with pirfenidone. Anti-fibrotic drugs should therefore be discussed in a patient with fibrosing ILD that worsens despite treatment.

Lung transplantation is a therapeutic option to be anticipated and prepared for in severe (FVC < 60% or DLCO < 40%) or progressive forms of pulmonary fibrosis in SD, in a subject under 65 years of age, with an otherwise controlled disease. Initial contact with a transplant team allows the issue to be discussed with the patient, the necessary assessment to be carried out and, in the event of acute respiratory deterioration, burdensome therapies such as extracorporeal membrane oxygenation to be considered as a bridge to transplantation.

Finally, in case of lymphoma and/or AA amyloidosis, treatment will be adjusted according to the nature of the lymphoid or plasma cell clone and the extent of the disease.

6.3.3.2.8. Neurological manifestations.

Peripheral nervous system damage. As discussed above, the choice of treatment for peripheral nervous system involvement in SD depends on the type of involvement, its severity and its progression.

Again, a distinction must be made between disorders linked to cryoglobulinaemic vasculitis, which can cause multiple mononeuropathy, and distal, painful, ascending polyneuropathies, of ten asymmetric, most often with motor impairment. The treatment is then that of vasculitis (see dedicated section).

The 2nd framework concerns disorders that only justify symptomatic treatment (co-antalgic treatment). This includes pure sensory polyneuropathies, isolated trigeminal neuralgia and SFN. The latter, which is accompanied by a normal electromyogram (EMG), must be confirmed by a skin biopsy. In case of very disabling trigeminal neuralgia, a medium dose of corticosteroids (0.2 to 0.3 mg/kg/day) may be offered. In case of objectively progressive sensory polyneuropathy, treatment with an immuno-suppressant may be discussed in the multidisciplinary meeting within the reference/competence centres. A trial comparing intravenous immunoglobulins to placebo is under way in sensory or sensory-motor neuropathy.

Finally, the 3rd framework concerns chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and ganglionopathies. In CIDP outside the specific context of SD, there is a positive randomised controlled trial demonstrating the benefit of monthly intravenous immunoglobulins administered at a dose of 2 g/kg over 4 days, versus corticosteroids. This trial and retrospective series in SD support the use of intravenous immunoglobulins in CIDP in SD. In contrast, the literature is less supportive of the use of intravenous immunoglobulins in lymph node disease. Based on expert recommendations and case series, the alternatives in severe forms are bolus corticosteroids or immunosuppressive therapy with mycophenolate mofetil or cyclophosphamide. In some forms of autoantibody-associated lymph node disease (not routinely available), rituximab may be offered. Given the potential severity and the limited literature on this type of neuropathy, it is strongly recommended that the treatment of these neuropathies be discussed on a case-by-case basis in the multidisciplinary meeting of the reference/competence centres.

Autonomic nervous system disorders may be associated with Sjögren's neuropathies but remain relatively rare and are not the subject of specific therapeutic indications apart from their symptomatic management.

Central nervous system damage.

Central nervous system (CNS) involvement is very rare in SD and therefore the grade of recommendations for the treatment of these different manifestations is low. In the first instance, a search should be made for genuine multiple sclerosis, which may be associated with SD (to be discussed in a multidisciplinary meeting). Sometimes the type of involvement is different and 4 types can be distinguished:

- multiple sclerosis-like disease but with atypia for typical multiple sclerosis, with white matter abnormalities in the periventricular, juxtacortical, subtentorial or medullary areas. Treatment may follow the recommendations for the management of typical multiple sclerosis. It should be noted that the option of anti-CD20 treatment, whose efficacy has been established in multiple sclerosis, seems valuable in the context of SD, particularly in the presence of other systemic disorders of SD, and should be discussed in a multidisciplinary manner;

- vasculitis-like involvement of the CNS. In this situation, treatment is based on the administration of corticosteroid boluses combined with cyclophosphamide;

- neuromyelitis optica (NMO) or its spectrum (NMOSD/neuromyelitis optica spectrum disorders), which is associated with autoimmune diseases (myasthenia gravis, lupus, SD) in about 30% of cases. When a patient with SD has an optico-spinal presentation (myelitis or optic neuritis), or even brainstem involvement (relatively frequent in NMOSD), anti-AQP4 antibody testing should be systematically performed. However, the impact of these autoimmune disease associations is rather limited. Indeed, there are no really validated molecules for the treatment of neurological SD, contrary to NMOSD for which several phase III studies with monoclonal antibodies have shown excellent efficacy with a 70 to 80% reduction in the risk of relapse. These molecules have a different mechanism of action: anti-CD20/CD19 for rituximab and in ebelizumab, anti-IL6receptor for satralizumab and anti-

complement for eculizumab. Satralizumab has been tested in patients with NMOSD associated with autoimmune diseases and in particular SD with no difference in efficacy. Therefore, it seems logical to offer this type of treatment to patients with NMOSD alone as well as those with associated SD;

•rarely, myelitis may be observed as transverse or more diffuse myelitis. Myelitis must be distinguished from a diffusion of the inflammatory signal from the posterior ganglion to the medulla in case of ganglionopathy. Treatment is based on corticosteroid boluses associated with cyclophosphamide.

6.3.3.2.9. Haematological manifestations. Cytopenia.

A decrease in the different lineages can be observed in SD.

Lymphopenia is a sign of activity in SD and does not require specific treatment, in particular, prophylaxis with sulfamethoxazole/trimethoprim is not recommended in isolated lymphopenia in SD outside the context of additional drug immunosuppression.

SS-related neutropenia is relatively rare. It may be related to excessive margination (which can be uncovered by a stress test). It may also be related to large granular lymphocyte proliferation (LGL) of the T-LGL type or to autoimmune neutropenia. In both situations, symptomatic treatment with G-CSF is warranted if there is an infection and/or a neutrophil count below $500/\text{mm}^3$. In case of neutropenia related to LGL proliferation, methotrexate may be used at a dose of 0.3 mg/kg per week. It should be introduced in progressive doses, with close monitoring of the CBC and covered by G-CSF.

In case of autoimmune thrombocytopenia (ITP), treatment will be considered from a threshold of less than $30,000$ platelets/ mm^3 , the risk of bleeding being extremely rare beyond that. In case of autoimmune haemolytic anaemia (AHAI), treatment will be considered for haemoglobin levels below 10 g/dL. In these two situations, and in accordance with the recommendations proposed by EULAR, the first-line treatment is systemic corticosteroids at a dosage of 0.5 to 1 mg/kg/day with progressive reduction. For ITP, a short course of treatment is usually sufficient (1 month); for AHAI a longer course of treatment over 3 months is usually required. In the event of failure or more profound anaemia (< 8 g/dL), rituximab is the treatment to be offered according to the 1 g D1–D15 administration schedule. It should be noted that the expected onset of action is approximately 2 weeks. Also, in emergency situations, particularly in case of ITP with bleeding, treatment with intravenous immunoglobulins 1 g/kg on D1 and D2 will be offered in accordance with the recommendations of the ITP 2017 NDP.

Lymphoma. The occurrence of B-cell lymphoma is one of the most severe complications in SD. These are typically B-cell lymphomas, preferentially of the marginal zone type with a pre-dominantly extra-nodal location: MALT lymphoma. High grade diffuse large B-cell lymphoma (DLBCL) is the most common histological type.

In case of low-grade lymphoma, it has long been suggested that treatment should simply be withheld. However, despite the indolent course of these haematological malignancies, it must

be emphasised that they occur in patients with a generally very active form of the disease, thus corresponding to only the tip of the iceberg of B lymphocyte hyperactivation. Thus, in contrast to indolent MALT lymphomas without underlying autoimmune disease, treatment should usually be discussed in case of other associated systemic manifestations. This is in line with the European Society for Medical Oncology (ESMO) guidelines, which emphasise that chemotherapy should be offered in MALT lymphoma associated with symptomatic systemic disease. The recommendation is to combine rituximab therapy with an alkylating agent (chlorambucil or bendamustine) or a purine analogue such as fludarabine. The combination of rituximab and bendamustine has been evaluated in a retrospective series of MALT lymphomas complicating SD with a good safety and efficacy profile and a reduction in the overall activity of SD. Unlike in follicular lymphoma, maintenance treatment with rituximab is not recommended due to the risk of iatrogenic hypogammaglobulinaemia and the lack of data supporting improved efficacy. In fragile patients (age > 80 years old, multiple comorbidities) or in localised forms without systemic signs, rituximab alone may be a treatment option.

The treatment of DLBCL follows the recommendations for the general population, i.e. in 1st line a polychemotherapy of the R-CHOP or R-ACVBP type.

The choice of treatment should be validated by a haematology multidisciplinary meeting with the participation of the autoimmune disease specialist.

6.3.3.2.10. Gastrointestinal disorders.

Autoimmune pancreatitis has been described but most of it is actually related to the differential diagnosis of SD, IgG4-associated disease.

Primary biliary cholangitis and autoimmune hepatitis may be associated with SD and should be investigated in case of liver function abnormalities.

Gastrointestinal complaints are frequently reported by patients. However, there are no studies demonstrating a higher frequency than in the general population and a direct link with SD.6.4. Therapeutic patient education and lifestyle modification

6.4.1. Definition

Therapeutic patient education (TPE) is a key element of comprehensive patient care. This approach, which must be multidisciplinary, has been defined by the World Health Organisation as follows:

- “TPE aims to help patients acquire or maintain the skills they need to manage their livings with a chronic disease as well as possible;
- it is an integral and permanent part of the patient’s care. TPE includes a programme with several workshops defined by the TPE team (e.g. SD and dryness, SD and fatigue, SD treatments), which aims to empower the patient in relation to their symptoms. This aims to help them (and their families) understand their disease and treatment, work together and take

responsibility for their own care in order to help them maintain and improve their quality of life;•oral or written information and preventive advice can be given by a healthcare professional on various occasions, but they are not equivalent to TPE.”;

•“the educational approach is participatory and person-centred, not simply the transmission of knowledge or skills.”;

•“it is a partnership between the patient, his or her family and the health care team, with the aim of helping the sick person to take care of him or herself.”;

•TPE contributes to the improvement of the health and quality of life of the patient and their relatives.

The specific aims of TPE are:

•the patient’s understanding of the nature of their condition and its possible consequences;

•the acquisition and maintenance of self-care skills by the patient:

- relieving symptoms,
- taking into account the results of self-monitoring, self-measurement, adjusting medication doses,◦ carrying out technical and care procedures,
- implementing lifestyle changes (balanced diet, physical activity, etc.),
- preventing avoidable complications,
- coping with the problems caused by the disease,
- involving those around you in the management of the disease, its treatment and its consequences,
- mobilisation or acquisition of coping skills,
- knowing yourself, having confidence in yourself,
- knowing how to manage your emotions and control your stress,
- developing creative thinking and critical reflection,
- developing communication and interpersonal skills,
- making decisions and solving a problem,
- setting goals and making choices,
- observing, evaluating and strengthening each other.

It is important to remember that information and therapeutic patient education do not have the same objectives:

The first one's is to provide information to a "passive" patient. It is part of the duties of every doctor and is a right of the patient (Law of 4 March 2002).

The "educational" dimension goes further because receiving information about the disease does not mean learning to live with it. TPE is based on the "active" approach of a patient who questions, reacts, expresses him- or herself, exchanges with a healthcare professional and/or with peers. Each person is unique, each situation is unique. This personalised and benevolent "support" helps the patient to make decisions about care, which is sometimes difficult and complicated, in order to improve his or her quality of life and thus that of his or her family. It also helps them to make choices concerning their life project, their orientation, their administrative files, etc.

6.4.2. Content of therapeutic education

The HAS has issued guidelines to assist in the implementation of educational programmes or approaches.

Thus, TPE consists of 4 stages:

- elaboration of an individualised educational diagnosis (shared educational interview) with the patient, which allows them to define their needs – expectations – fears – beliefs – projects. . . ;
- definition of a personalised TPE programme that defines the "skills" (self-care and coping skills) that the patient can acquire and/or mobilise; or participation in TPE groups according to the patient's choice;
- planning and implementation of TPE sessions that use highly codified content and learning methods;
- assessment of achievement at the end of the educational programme (individual "skills" assessment).

To date, only a few teams have developed therapeutic education programmes in SD (<https://www.fai2r.org/les-pathologies-rares/gougerot-sjogren/etp>).

The most detailed programme validated by the ARS is the SESAME programme built and developed by the rare disease reference centre of the Paris-Saclay University Hospitals.

During the development of this programme, the educational objectives and skills to be acquired by the patients targeted by TPE in the field of SD were defined (Fig. 15), and are summarised in Table 8.

In this context, within the framework of SD, a specific questionnaire for patients has been developed. It can be used before and after the educational programme. Before, it can be used to assess the skills of SD patients and to help with the educational diagnosis. After, it helps to assess the achievements of the educational programme. This questionnaire is available online

on request from the reference centre of the Paris-Saclay University Hospitals (crmr.sjogren@aphp.fr).

6.4.3. Books for patients

There is often a lack of awareness of this rare disease among GPs, other specialists and many healthcare professionals. Patients therefore have a fundamental role to play in their own care. In this context, therapeutic education has a major role to play in enabling the patient to be a stakeholder in his or her own care and management. Access to therapeutic education sessions is however limited by their availability (few centres and few sessions).

The information available in the mainstream media and on the internet is extensive and sometimes erroneous. For this reason, a book for patients has been written by physicians who are experts in the disease in collaboration with patients: “Sjögren’s in 100 questions” (available only in French).

6.5. Use of patient organisations

Healthcare professionals and patients should be informed about the existence of Patient Associations. These organisations contribute to better overall management of the disease by promoting cooperation between patients, patient associations and carers.

The French Association of Gougerot-Sjögren’s and Dry Syndromes (AFGS) is a non-profit association, created in 1990, recognised as promoting the public interest and approved by the Ministry of Health to represent users in hospital or public health bodies (<https://www.afgs-syndromes-secs.org/>).

The AFGS’s mission is:

- to provide information on Sjögren’s disease and dry syndromes;•to provide financial support for medical research;
- to provide moral support to patients;•to enable patients to meet each other.

The AFGS offers a number of services to all people affected by Sjögren’s disease and/or dry syndromes: telephone support, quarterly newsletter, documentation, regional meetings, medical conferences, topic forums, etc.

In its public section, the AFGS website provides information to patients and their families, general practitioners and Internet users seeking information on Sjögren’s disease, dry syndromes or the AFGS. The medical information provided on this site is not a substitute for the patient–physician relationship.

7. Follow-up [5, 6 8, 14, 22, 36, 52, 73]

SD frequently leads to significant impairment of quality of life through its classic triad (dry syndrome, fatigue and pain). It may also be accompanied by visceral or biological complications as reported in the ESSDAI activity score (see Appendix 2). In France, primary Sjögren’s disease is considered a rare disease with a prevalence of 1/1000 to 1/10,000. The

management and follow-up of patients is therefore the responsibility of centres and doctors with good expertise in the disease. Depending on the initial assessment, a personalised follow-up plan can be established, based on the clinical and biological phenotype carried out at diagnosis or at the time of the first treatment.

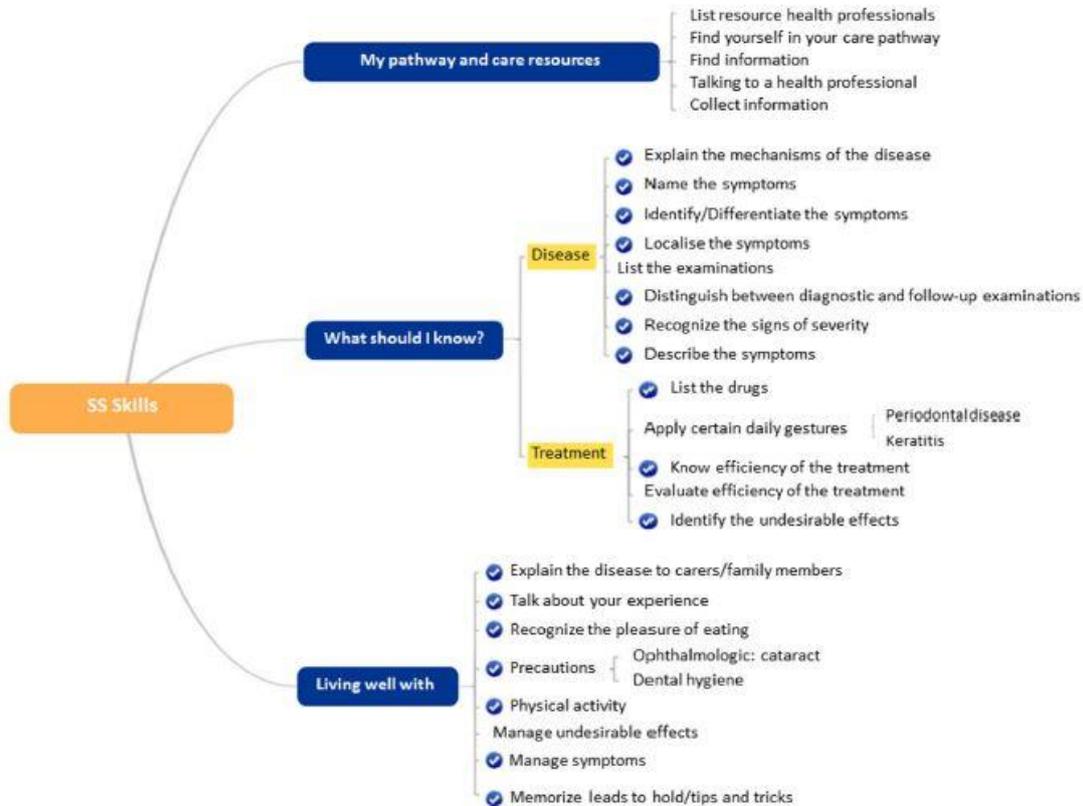


Fig. 15. Competency framework of the Sjögren's disease (SD) TPE programme.

7.1. Objectives

The objectives are:

- to specify the activity and severity of the disease;
- to screen for sub-clinical visceral damage and potential biological complications;
- to assess the efficacy and tolerability of treatments;
- to look for a potential comorbidity;
- to assess vascular and infectious risk factors and risk factors for lymphoma.

7.2. Professionals involved (and coordination arrangements)

The consultations required in the care pathway depend on the initial assessment and the evolution:

- centre of reference, centre of competence, centre of expertise(internists, rheumatologists, ophthalmologists, stomatologists, pneumologists, ENT specialists, dental or oral surgeons, nephrologists, dermatologists, gynaecologists, paediatricians, etc.);
- attending physician;
- potentially depending on the clinical situation: psychologists, pain relief centres, dieticians, physiotherapists, social workers, etc.

7.3. Frequency and content of consultations

The frequency of consultations and the carrying out of tests (Tables 9 and 10) should be adjusted according to:

- the patient's clinical condition during the initial assessment and follow-up visits;
- disease activity, organ damage and disease severity;
- comorbidities;
- the treatments used (monitoring, tolerability, adverse events).
- every 3 to 6 months in case of SD with signs of activity on ESSDAI score;
- every 1–3 months in case of pregnancy, especially if there are anti-SSA/SSB antibodies;
- once a year or every 2 years in quiescent or mildly phenotypic forms.

The follow-up clinical examination is identical to the one carried out during the initial assessment and will be adjusted according to the functional signs, which it is important to question the patients about. The frequency of consultations is adjusted according to clinical evolution.

However, the frequency of consultations varies according to the initial severity, the type of visceral damage and/or the occurrence of intercurrent events. A clinical examination is necessary for each change in treatment. During each clinical examination, particular attention should be paid to:

- the severity of the triad associating dryness, pain, fatigue (with if possible collection of the ESSPRI score: 3 very simple VAS) and its psychosocial, professional and family repercussions;
- the potential occurrence of repeated episodes of parotidomegaly;
- the potential occurrence of repeated flare-ups of vascular purpura;

- the potential occurrence of any symptoms that would point to organ damage;
- height-weight growth in children.

Table 8
Educational objectives of the SESAME workshops.

What is SD?
To be able to explain to yourself and your relatives in your own words the mechanism of the disease (chronic nature, autoimmune mechanism, evolution by relapses, daily manifestations, etc.)
To give meaning to compliance with medical monitoring. The patient must have information on the so-called routine tests for the follow-up of his or her illness, in order to understand their necessity and importance, to follow the schedule when it exists and/or to anticipate it
To know how to list resource healthcare professionals
To use patient associations
Recognising the symptoms of SD and signs of severity
To acquire knowledge about the disease
To understand the tests used to make the diagnosis (search for dry syndrome, biopsy of the accessory salivary glands, autoantibodies)
To acquire knowledge and safety skills in relation to signs of severity (e.g. massage of the parotid glands in case of painful swelling)
To understand laboratory tests in order to look for signs of severity (so-called systemic disorders affecting an organ)
To know how to differentiate between symptoms that are related to SD and those that are not
Living with SD
To express your experience of living with the disease, your own representations, your suffering. Acceptance of the chronic disease. To improve quality of life
To clarify your own emotions
To better manage fatigue
To better manage pain
To identify personal and external resources to be mobilised in response to the difficulties encountered
To discover new resources that can be used; consider personal strategies
To allow yourself to make plans to live better with Sjögren's disease
Dry mouth syndrome
To have a balanced diet and rediscover the pleasure of eating
To identify your own signs and symptoms
To understand the role of saliva and the consequences of dry mouth
To identify different treatment and lifestyle strategies
To develop skills in tooth brushing and salivary gland massage
Dry eye syndrome
To better understand the mechanisms of dry eye syndrome
To identify the different treatment approaches
To know how to do eyelid care and improve the use of eye drops
To know the complications of dry eye syndrome
Treatment and treatment protocols
To know how to differentiate between background and symptomatic treatment
To acquire knowledge of general and local treatments according to the manifestations of the disease
To understand what a therapeutic protocol is and be able to participate in it

SD: Sjögren's disease.

The physical examination will systematically include:

- examination of the mouth for complications of dry syndrome (mycosis, etc.);
- parotid and submandibular examination;
- looking for painful and swollen joints;
- lung auscultation;

- looking for hepatosplenomegaly;
- a general review.

Table 9
Frequency and indication of laboratory tests to be performed during the follow-up of a patient with Sjögren's disease.

Type of test	Indication
At each visit	
CBC with platelets	
Blood ionogram, creatinine and glomerular filtration rate	
CRP	
Proteinuria/creatinuria ratio on sample (and potentially urine cytobacteriological test)	Standard laboratory testing
Albumin levels, liver function tests (AST, ALT, γ GT, total bilirubin and alkaline phosphatases), CPK	
Protein electrophoresis, weighted IgG assay	Testing for a monoclonal component and hypergammaglobulinaemia
Rheumatoid factor; C3, C4; Cryoglobulinaemia	If cryoglobulinaemia is positive initially or there is clinical evidence of progression or vasculitis or glomerular kidney disease
Non-systematic	
LDH	In case of suspected lymphoma
TSH	According to clinical data and history
HCV, HBV and HIV viral serologies	If the introduction of immunosuppressive therapy or biologic therapy is being considered
QuantIFERON	
Testing for anti-SSA/SSB autoantibodies	Does not need to be repeated during follow-up if initially positive. In view of pregnancy, a new test for anti-SSA/SSB antibodies may be carried out if they were negative at the initial assessment
Circulating anticoagulant, anti-cardiolipin and anti-beta2GPI antibodies	To be performed if not done in the initial assessment. Not to be repeated during follow-up, unless there is a new thromboembolic or obstetrical clinical finding, or in view of a pregnancy
Comorbidities	
Fasting blood glucose	Testing for associated comorbidities
Testin for lipid abnormalities	
Gynaecological examination and smear test	Cervical cancer screening Every year if taking immunosuppressants or biologic therapy At the rate of the general population in other cases: in women aged 25 to 65 and every 3 years after 2 normal smears performed at 1 year intervals In case of long-term corticosteroid therapy every 3 years
Bone densitometry	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CBC: complete blood count; CPK: creatinine phosphokinase; CRP: C-reactive protein; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; LDH: lactate dehydrogenase; TSH: thyroid-stimulating hormone.

7.4. Paraclinical testing

The frequency of these tests, as well as the prescription of other additional laboratory tests, is adjusted according to:

- the patient's clinical condition;
- disease activity, organ damage and disease severity;

- comorbidities;
- treatments.

These tests aim to:

- monitor and detect specific, sometimes asymptomatic disorders (particularly biological, such as cytopaenia, monoclonal component, ionic disorders or interstitial or glomerular renal damage)or signs of progression to lymphoma;
- detect complications of treatments and to look for the occurrence of newly associated comorbidities;
- detect the occurrence of an overlap syndrome (association with another connective tissue disease).

The systematic laboratory tests to be carried out at each visit ar eto be adjusted according to the clinical and biological phenotype defined during the initial assessment.

7.4.1. Cardiorespiratory damage

The cardiorespiratory damage have:

- pulmonary function tests with DLCO:
 - in case of interstitial lung disease, to be performed every year or more frequently (every 3 to 6 months) in case of severe or progressive interstitial lung disease. The 6-minute walk testis performed every 6 to 12 months in case of severe or progressive interstitial lung disease. It assesses exercise tolerance.

Follow-up PFTs are generally not helpful in case of bronchial or bronchiolar involvement;

- high-resolution, injection-free, low-dose thoracic CT scan:
 - systematic in case of unexplained acute or subacute exacerbation of previously diagnosed interstitial lung diseases,
 - in the assessment of newly acquired clinical lung disease or dyspnoea not explained by another cause;
- bronchial endoscopy with bronchoalveolar lavage, usually not necessary during follow-up:
 - it should be performed during the course of the disease if infiltrates or pulmonary nodules appear, and if there is any doubt as to whether the ILD is progressive or an infectious complication,
 - no indication for routine bronchoalveolar lavage during follow-up of interstitial lung diseases;

- electrocardiogram (ECG) in case of cardiac symptoms;
 - cardiac ultrasound if dyspnoea or symptoms suggestive of peri-carditis occur and at the slightest cardiac symptom
- Holter ECG if a heart rhythm or conduction disorder is suspected.

7.4.2. Other systemic disorders

The other systemic disorders are:

- renal ultrasound, renal function tests, renal biopsy in case of suspected interstitial or glomerular damage;
- ultrasound of the main salivary glands: although salivary ultra-sound can be a diagnostic aid in the initial work-up, regular ultrasound monitoring is not recommended except in case of anew clinical episode, persistent parotidomegaly, or recent asymmetric parotid swelling;
- ultrasound of the joints, hands and wrists may be useful in case of joint inflammatory, mechanical or mixed pain without clinical evidence of synovitis. Ultrasound may be more effective than clinical evidence of synovitis;
- EMG in case of clinical muscle deficit or CPK elevation, or in case of clinical signs of sensory or sensorimotor neuropathy;
- brain MRI in case of cranial nerve damage, central neurological symptoms, looking for inflammatory signs.

7.4.3. Suspicion of lymphoma

If lymphoma is suspected, the following tests should be per-formed:

- serum protein electrophoresis and immunofixation. In case of proteinuria, electrophoresis and immunofixation of urine proteins;
- serum free light chains;
- β 2-microglobulinaemia;
- cryoglobulinaemia; LDH;
- PET scan;
- if PET scan is difficult to access: neck, chest, abdomen and pelvis CT scan;
- parotid ultrasound if asymmetrical/persistent parotidomegaly;
- a new biopsy of the accessory salivary glands which can be a simple way of revealing lymphoma especially if the suspicion is made in the presence of a persistent parotid or submandibular hypertrophy;

- if biopsy of the accessory salivary glands has not shown lymphoma, a parotid biopsy under ultrasound if it is a parotid nodule;
- node biopsy and/or ultrasound- or CT-guided mass biopsy in case of node location.

These tests will never be carried out systematically, but only in case of suspicion of lymphoma.

8. Pregnancy [83,84,95–100]

8.1. Contraception and fertility

Contraception and fertility preservation should be considered in young patients in whom systemic involvement raises the possibility of teratogenic treatments or treatments that impair fertility (immunosuppressants or anti-fibrotic drugs).

Any type of contraception can be used. In particular, in the absence of other associated autoimmune pathologies (systemic lupus, antiphospholipid syndrome), there are no contraindications to oestrogenic contraceptives, provided that their conditions of use are followed.

The fertility of women with SD is not different from that of a control population in the various studies available.

8.2. Impact of SD on pregnancy

8.2.1. Obstetrical complications

The data in the literature on the impact of SD on the occurrence of obstetrical events is scarce, based on retrospective studies with small numbers of patients. Based on this data, early spontaneous miscarriage seems to be slightly more frequent, possibly linked to the more advanced age of the mothers. Some studies find a higher rate of prematurity (birth < 35 weeks of gestation). Other studies find a higher rate of low weight for gestational age and a higher rate of caesarean sections. Pregnancies carried to term and without complications are, however, the most common.

8.2.2. Specific risk of anti-SSA/SSB antibodies: neonatal lupus

Neonatal lupus is a syndrome manifested by skin, haematological, hepatic or cardiac involvement. Cardiac manifestations include congenital atrioventricular block (cAVB) occurring in a heart free of malformations and disease, and more rarely, endomyocardial fibroelastosis or late cardiomyopathy. This syndrome observed in the foetus or in the newborn is associated with the presence in the mother of anti-SSA antibodies (Ro 60 and/or 52) associated or not with anti-La/SSB antibodies.

While skin, liver and haematological damage is usually transient, cardiac damage, and in particular cAVB, is permanent, with a mortality rate of around 20% (10% in utero, 10% postnatal).

The frequency of occurrence of neonatal lupus, and in particular cAVB, in a newborn of a mother with anti-SSA/SSB antibodies is estimated to be between 0.7% and 2%, with a higher risk of recurrence (17% to 19%) in case of cAVB in a previous pregnancy, a risk that can probably be reduced by treatment with HCQ (see below). This complication most often occurs between 14 and 24 weeks of gestation.

Based on published data from the French cAVB registry, bear in mind that the diagnosis of this syndrome is made in newborns whose mothers are free of any known pathology in the vast majority of cases, the minority of them having previously suffered from systemic lupus, overlapping connectivity or SD.

8.2.2.1. In utero screening for cAVB.

In patients with SD and anti-Ro/SSA antibodies, it is still often suggested to monitor foetal heartrate every two weeks between 14 and 24 weeks of gestation, bearing in mind that this screening shows no abnormality in 99% of cases, and above all that in case of cAVB, no curative treatment has been validated (cf. infra). Moreover, the psychological burden of these six successive ultrasound scans in two months is heavy and can be a source of anxiety for patients. Thus, some teams have lightened this protocol with only one additional foetal ultrasound at 26 weeks of gestation in addition to the typical pregnancy ultrasound at 20 weeks of gestation. In patients with SD who have had a previous pregnancy with a complication such as cAVB, this screening can be done weekly during the same period, from 14 and 24 weeks of gestation.

8.2.2.2. Curative and preventive treatment of cAVB.

A “curative” treatment of cAVB detected in utero with fluorinated corticosteroids (dexamethasone, more rarely betamethasone) has long been suggested. However, a recent meta-analysis reports no benefit, and this treatment is no longer recommended. The only management is based on monitoring of the pregnancy and delivery in a specialised paediatric cardiology centre.

In a recent study, HCQ (400 mg/d) may be effective in preventing recurrence of AVB in women with a history of pregnancy with cAVB. This treatment, introduced no later than 8 weeks of gestation, reduced the risk of recurrence of cAVB in a subsequent pregnancy by about 50% compared with what was expected in the literature. These results were confirmed by the prospective PATCH study. It therefore seems logical to offer HCQ to all women with a previous pregnancy with cAVB.

In the absence of a history of cAVB and in an anti-SSA positive patient with no other indication for HCQ treatment, and given the rarity of this complication, it is not currently recommended to initiate this treatment preconceptionally or at the beginning of a pregnancy, although this can be discussed with the patient.

8.3. Impact of pregnancy on SD

Pregnancy does not seem to influence the evolution of SD. Unlike systemic lupus, there is no evidence in the literature that SD worsens during pregnancy. Thus, it is important to reassure young women with SD that there will be no medical obstacles to a planned pregnancy. However, considering that younger patients of childbearing age generally have a higher clinical and biological activity profile than those diagnosed later, multidisciplinary follow-up is warranted during pregnancy and postpartum.

8.4. Care during pregnancy

8.4.1. Preconception consultation

This consultation is mainly for SD patients with visceral manifestations, receiving background treatment, and for those with anti-SSA/SSB antibodies or antiphospholipid syndrome.

The objectives of this preconception consultation are:

- to define any formal contraindications to pregnancy, which are very rare in this disease (pulmonary arterial hypertension, severe renal insufficiency with specific nephropathy, severe respiratory insufficiency, in particular);
- to adjust the background treatment (CRAT website:<http://www.lecrat.fr/>). The maintenance and/or introduction of HCQ treatment is possible. Corticosteroid therapy can be maintained if necessary, using a minimally effective dose in order to limit the side effects induced and notably the occurrence of gestational diabetes. If it was not necessary before, there is no reason to introduce corticosteroid therapy in anticipation of pregnancy. Teratogenic immunosuppression should be discontinued (methotrexate, mycophenolate mofetil, leflunomide) in favour of a non-teratogenic immunosuppressive treatment (azathioprine+++, ciclosporin, tacrolimus);
- to check vaccination status (renew rubella vaccine if serology negative and if no contraindications, whooping cough, seasonal flu and COVID, according to current recommendations);
- if the patient is a carrier of anti-SSA/SSB antibodies, explain to the couple how to monitor for neonatal lupus, a very rare complication;
- to diagnose potential associated autoimmune diseases:
 - autoimmune thyroiditis, more common in SD, sometimes requiring preconception levothyroxine and regular monitoring of thyroid function during pregnancy,
 - antiphospholipid syndrome or even isolated antiphospholipid antibodies., to be looked for in particular in case of repeated miscarriages, a suggestive obstetrical history (pre-eclampsia, intrauterine growth retardation, foetal death in utero), or a previous thrombotic event (see NDPC lupus).

Folic acid supplementation should also be started as in any conventional pregnancy.

8.4.2. During pregnancy

In addition to standard monthly clinical and ultrasound gynaecological monitoring, specific foetal heart ultrasound monitoring may be offered (see above).

Clinical monitoring of the underlying pathology should also be offered and potential signs of activity should be sought. The frequency of this clinical monitoring should be adapted to the severity of the connective tissue disease. A specialised consultation per quarter is desirable in addition to gynaecological monitoring.

Laboratory-based monitoring focuses on the type(s) of preexisting organ damage and/or associated pathology: blood count, creatinine levels, ionogram, TSH, proteinuria, blood glucose levels, rubella serology and/or toxoplasmosis serology if negative. Hydroxychloroquine levels may be useful in patients on HCQ to assess adherence to treatment.

8.5. Childbirth and postpartum

Apart from performing an electrocardiogram on the newborn in the first 3 days of life and avoiding the sun (to prevent cutaneous neonatal lupus), (if the mother is a carrier of anti-SSA/SSB antibodies), there are no specific measures.

8.6. Breastfeeding

Breastfeeding is most often possible and recommended, provided that the treatments are *compatible, which is most often the case* (CRAT website: <http://www.lecrat.fr/>).

9. Paediatrics

9.1. General

SD may appear in childhood but it is a very rare manifestation, with a polymorphic clinical presentation and can be therefore easily under-diagnosed. The ratio remains predominantly female with 7–8 girls to 1 boy. The average age of onset is 8 years old (4–10 years old). Although dryness is common (around 30–50%), it can be difficult to diagnose in young children. Other manifestations are often in the foreground, such as involvement of the major salivary glands (uni- or bilateral parotitis) or adenopathy. The diagnosis is most often made on the basis of a combination of clinical and paraclinical arguments, since the classification criteria for adults are not fully adapted to the paediatric form (an international group is working on proposing paediatric criteria) and the tests are sometimes not feasible. Ultrasound of the salivary glands is important here as it is frequently pathological but not invasive. Treatment is currently similar to that recommended for adults with particular attention given to oral hygiene.

9.2. Diagnosis

Main objectives:

- to detect and assess dry eye and mouth;
- to suggest a diagnosis of SD in the presence of various systemic disorders;
- to look for associated diseases;
- to make the differential diagnosis with xerostomia or salivary damage of other origin.

Professionals involved (coordination arrangements):

- paediatric rheumatologist;
- paediatrician;
- dental surgeon – oral surgeon;
- ophthalmologist;
- other organ specialist depending on the condition;
- reference or competence centre for SD.

9.2.1. Diagnosis

The diagnosis will be based on clinical data and additional testing. There are no validated classification or diagnostic criteria for children and the criteria developed for adults are not suitable either because of the often more systemic clinical presentation in children or because of the difficulties in objectively gathering evidence of and testing for dryness.

Complaints of dryness are sometimes absent in early life, especially before the age of 6, and poorly correlated with the results of additional tests.

It will be important to look for complications related to hyposaliva to avoid the development of caries.

In children, systemic (i.e. non-dryness) involvement is prominent in over 50% of cases. The most frequent is uni- or bilateral parotidomegaly. It is often confused with mumps lesions, which are rarely recurrent. Musculoskeletal disorders (20%, arthralgia, myalgia), polyadenopathy, systemic disorders (unexplained fever) and renal disorders (hypokalaemia) are also found in children (Table 11).

When the initial presentation is parotidomegaly, particularly unilateral, infectious aetiologies should be considered and an ENT specialist consulted for the initial diagnostic discussion (Table 12).

The diagnosis of paediatric SD is based on questioning, clinical and paraclinical testing.

Table 11
Non-exhaustive list of systemic conditions in paediatric Sjögren's disease.

Juvenile onset systemic Sjögren's disease		
Domain	Frequency	Type of involvement
Salivary glands	50 to 75%	Recurrent uni- or bilateral parotitis
Laboratory-measured damage	60 to 100%	Hypergammaglobulinaemia, cytopaenia
Constitutional	20%	Fever
Joint	10 to 20%	Arthralgia or arthritis, diffuse pain
Kidneys	10%	Tubular acidosis, hypokalaemia, interstitial nephritis, glomerulonephritis
CNS	9%	Vasculitis, ataxia, hemiparesis, aseptic meningitis, polyradiculoneuritis, headache, ptosis
Lymphadenopathies	10 to 15%	
Skin	5%	Exanthema, rash, dryness, nodules
Lung	2.5%	Interstitial lesions
Muscles		Myositis
Gastrointestinal disorders		Pancreatitis, cholestasis
Raynaud	30%	

CNS: central nervous system.

Table 12
Non-exhaustive list of differential diagnoses of inaugural parotidomegaly.

<p>Infectious parotidomegaly, often unilateral (bacterial: streptococcus viridans, haemophilus influenzae. Viral: mumps Epstein-Barr virus, HIV, coxsackies) Bilateral: IgG-4, sarcoidosis and other granulomatoses, anorexia nervosa, diabetes, recurrent juvenile parotitis, lymphoma</p>
HIV: human immunodeficiency virus.

9.2.2. Epidemiological data

This data is from retrospective cohorts. The ratio is 8 girls/1 boy, with an average onset of symptoms between 8 and 10 years old, but a diagnostic delay of 2 years. However, the disease can begin much earlier, as early as 4 years old.

9.2.3. Clinical examination in children

The questioning, clinical examination and serological tests are identical to those performed in adults. However, weight and height measurements are systematically taken and reported in the health record (in particular to ensure that there is no interruption in the height-weight curve).

9.2.4. Dryness

Dry eyes and dry mouth are present in 30–70% of cases, but unlike in adults, they are not always in the foreground. Oral involvement leads to a sensation of dry mouth, glossitis, cheilitis and also caries despite satisfactory oral hygiene. Recurrent oral ranulas (in the absence of lingual trauma) may suggest the diagnosis.

Ocular involvement is similar to that of adults (dryness, sensation of sand in the eyes, ulceration, dry keratoconjunctivitis).

Skin and vaginal dryness have also been described in children.

9.2.5. Systemic disorders

Often in the foreground and present in over 50% of cases. The ESSDAI can be referred to for assessment but there are other potential rare manifestations as in adults with pancreatitis, cholestasis and cytolysis.

In adults, forms beginning before the age of 35 often come with systemic complications, with more associated autoimmune diseases. This prompts greater vigilance in paediatric onset forms.

The main systemic manifestation is unilateral or bilateral parotidomegaly which, when present at the beginning of the disease, should raise the question of differential diagnoses, particularly in the unilateral form (Table 12). Parents will often indicate that their child has had mumps several times. Laboratory-measured disturbances (hypergammaglobulinaemia, cytopaenia) are present in 60 to 100% of cases, constitutional damage such as fever in 10% of cases, joint damage in 20% of cases (Table 11). Lymphadenopathy is also common.

9.2.6. Additional testing

The additional testing consists of:

- autoantibodies: both SSA/Ro60 and anti-SSB are frequently positive in children, antinuclear antibodies may be present at high levels as well as rheumatoid factors;
- biopsy of the accessory salivary glands: it is perfectly feasible in children, notably from the age of 10. For younger children, it is more difficult to perform in practice. We can recommend the use of Entonox (equimolar mixture of oxygen and nitrous oxide) in nasal cannula, the use of virtual reality headsets or finally, to have the biopsy of the accessory salivary glands carried out during the parotid biopsy procedure if the latter is offered as part of the exploration of a parotidomegaly and therefore under general anaesthesia;
- ultrasound of the parotid and submandibular salivary glands allows for the study of parenchymal changes. Non-irradiating and painless, it is pathological in 60% of children, showing an inhomogeneous parenchyma and hypoechoic areas. It requires a trained ultrasound technician;
- ophthalmic tests exploring dryness: difficult to perform before the age of 6. Except for the slit lamp examination, the Schirmer test, vital dye instillations or the break-up test require collaboration, can be unpleasant and sometimes unfeasible;
- objective dry mouth tests: unstimulated and stimulated salivary flow according to the patient's age;
- after the age of 6, the tests are similar to those of adults, although it should be noted that in children there is a very poor correlation between subjective complaints of dryness and the tests performed.

9.2.7. Differential diagnoses.

The differential diagnoses are:

- dry eyes in children with rosacea, allergic conjunctivitis, nutritional deficiencies and intensive use of screens;
- the differential diagnoses described in adults should also be considered in children.

9.3. Management of paediatric SD

9.3.1. Main objectives

The main objectives are:

- to control symptoms;
- to monitor oral involvement;
- to monitor systemic damage;
- to ensure appropriate schooling.

9.3.2. Therapeutic education and transition

Therapeutic education includes most of the items described for adults and is adapted to the child's various levels of understanding. It is also aimed at parents or legal guardians, who are real partners in the treatment. It ensures that the child or adolescent and his or her parents have a good understanding of the disease, the treatments and their complications.

The transition period must be anticipated (talk about it around the age of 12–14), and formalised between 15 and 20 years of age in order to empower the patient with regard to the disease and to address specific points such as self-image, projection into the future and adherence to treatment.

Career and educational pathways should be discussed regularly, but particularly in adolescence.

Consideration should be given to adapting school and sports activities to the manifestations of the disease.

9.3.3. Treatments

The treatment is identical to that of adults, and is based on symptomatic treatments that do not generally have a marketing authorisation for paediatric use (see treatment section).Corticosteroids are sometimes used in low doses, particularly in recurrent parotitis, and HCQ may be offered if there is another associated connective tissue disease. Dental and oral health status should be monitored more frequently because of the rapid progression of caries. Fluoroprohylaxis can be offered in addition to hygienic. . . and dietaryadvice.9.4. Follow-up of paediatric SD

9.4.1. Objectives

The objectives are:

- to monitor oral status and complications;
- to monitor ophthalmic involvement;
- to evaluate the effectiveness of the treatments;
- to reassess and adjust the care if necessary;
- to set up a personalised support plan if necessary;
- adherence to the vaccination schedule (all studies show that the vaccination schedule for children with autoimmune disease is often not adhered to, even though vaccination in these children is recommended, effective and well-tolerated).

9.4.2. Frequency and content of consultation

In general, the recommended frequency of clinical examination is every 6 to 12 months in the quiescent period, more frequently in case of SD with progressive systemic disease, every 2 to 3 months.

This monitoring includes:

- a full clinical examination, bi-annual or annual laboratory tests;
- dental consultation every 6 months;
- ophthalmology consultation every year.

The aim of the follow-up will be to check the absence of: complications linked to ocular and oral damage, systemic damage or interruption in the height-weight curve and to adjust the symptomatic treatments if necessary depending on the damage and quality of life.

Schooling may be accompanied by a personalised support plan if necessary, which will be evaluated annually.

The recommended vaccinations must be carried out.

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The authors declare that they have no competing interest.

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Authors' contributions

VD, XM, AAB, SB, BC, DC, GN, JEG, EH, PL, VLG, RMS, JM, MO,AS, RS, NCC wrote the first draft of the manuscript and participated to writing. All authors participated to edition. All authors read and approved the final version of the manuscript.

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