EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies

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ABSTRACT

The therapeutic management of Sjögren syndrome (SjS) has not changed substantially in recent decades: treatment decisions remain challenging in clinical practice, without a specific therapeutic target beyond the relief of symptoms as the most important goal. In view of this scenario, the European League Against Rheumatism (EULAR) promoted and supported an international collaborative study (EULAR SS Task Force) aimed at developing the first EULAR evidence and consensus-based recommendations for the management of patients with SjS with topical and systemic medications. The aim was to develop a rational therapeutic approach to SjS patients useful for healthcare professionals, physicians undergoing specialist training, medical students, the pharmaceutical industry and drug regulatory organisations following the 2014 EULAR standardised operating procedures. The Task Force (TF) included specialists in rheumatology, internal medicine, oral health, ophthalmology, gynaecology, dermatology and epidemiology, statisticians, general practitioners, nurses and patient representatives from 30 countries of the 5 continents. Evidence was collected from studies including primary SjS patients fulfilling the 2002/2016 criteria; when no evidence was available, evidence from studies including associated SjS or patients fulfilling previous sets of criteria was considered and extrapolated. The TF endorsed the presentation of general principles for the management of patients with SjS as three overarching, general consensus-based recommendations and 12 specific recommendations that form a logical sequence, starting with the management of the central triplet of symptoms (dryness, fatigue and pain) followed by the management of systemic disease. The recommendations address the use of topical oral (saliva substitutes) and ocular (artificial tear drops, topical non-steroidal anti-inflammatory drugs, topical corticosteroids, topical CyA, serum tear drops) therapies, oral muscarinic agonists (pilocarpine, cevimeline), hydroxychloroquine, oral glucocorticoids, synthetic immunosuppressive agents (cyclophosphamide, azathioprine, methotrexate, leflunomide and mycophenolate), and biological therapies (rituximab, abatacept and belimumab). For each recommendation, levels of evidence (mostly modest) and TF agreement (mostly very high) are provided. The 2019 EULAR recommendations are based on the evidence collected in the last 16 years in the management of primary 2002 SjS patients and on discussions between a large and broadly international TF. The recommendations synthesise current thinking on SjS treatment in a set of overarching principles and recommendations. We hope that the current recommendations will be broadly applied in clinical practice and/or serve as a template for national societies to develop local recommendations.

INTRODUCTION

Sjögren syndrome (SjS), a systemic autoimmune disease that affects 1–23 persons per 10 000 inhabitants in European countries,[1] presents with a wide spectrum of clinical manifestations and autoantibodies. Antinuclear antibodies are the most frequently detected autoantibodies, anti-Ro/SS-A the most specific, and cryoglobulins and hypocomplementaemia the main prognostic markers.[2] The histological hallmark is a focal infiltration of the exocrine glands by lymphocytes, determined by minor labial salivary gland biopsy. The clinical scenario is dominated by sicca syndrome caused by immune-mediated glandular involvement, accompanied by fatigue, musculoskeletal pain and systemic features in a significant percentage of patients, and complicated by lymphoma in around 2%–5% of patients.[3] When SjS appears in a previously healthy person, the disease is classified as primary, while patients with concomitant systemic autoimmune diseases (SAD) are classified as associated (or secondary) SjS; since this distinction only reflects a clinical situation of autoimmune coexistence the term SjS will be throughout the manuscript. SjS patients make substantial use of healthcare services, with a mean annual total direct cost per patient ranging between £2200 in UK and US$20 000 in the USA.[4 5]

The therapeutic management of SjS has not changed substantially in recent decades[6] and is still based on symptomatic treatment of sicca

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symptomatology and broad-spectrum immunosuppression for systemic disease, with insufficient information on the differential efficacy and safety of the therapeutic options available.[7] Treatment decisions remain challenging in clinical practice, without a specific therapeutic target beyond the relief of symptoms as the most important goal. Therefore there is growing interest in the proposal of clinical guidelines by national scientific societies.[8–11]

In 2010, the European League Against Rheumatism (EULAR) promoted and supported an international collaborative study (EULAR SS Task Force) aimed at developing disease-specific activity indexes in SjS (EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and EULAR Sjögren's syndrome disease activity index (ESSDAI) scores),[12 13] which are now widely used both clinically and in research. A second project, the development of the first EULAR evidence and consensus-based recommendations for the management of patients with SjS with topical and systemic medications, was proposed and launched.

METHODS

After approval of the proposal by the EULAR Executive Committee, the convenor (MR-C) and co-convenors (CV, SB, XM) invited international experts with a solid history of clinical research in SjS (most of whom were previously involved in the ESSDAI/ESSPRI project) to form part of a Steering Committee (SC) and a Task Force (TF), which also included methodologists, patient representatives and individuals from all relevant professional groups (online supplementary appendix 1). The aim was to develop a rational therapeutic approach to SjS patients that would be useful for healthcare professionals, doctors in specialist training, medical students, the pharmaceutical industry and drug regulatory organisations following the 2014 EULAR standardised operating procedures.[14] Industry involvement was not permitted at any stage of the project.

Steering committee

The SC included 13 rheumatologists, four internal medicine, one primary care and one oral health specialists, one epidemiologist, one statistician, one healthcare professional representative and two patient representatives. The SC agreed on some principal considerations upfront: (a) The statements were termed 'recommendations' as opposed to 'guidelines' or 'points to consider' because they offer guidance, which needs to be tailored to meet individual requirements. (b) Some general rules and definitions (overarching principles, general recommendations, definition of sequential therapeutic schedules, severity or refractoriness) cannot be evidence-based and were, therefore based on consensus. (c) The remaining statements were evidence-based, that is, supported by the highest level of evidence possible, limiting statements based only on retrospective data (although for some clinical or therapeutic scenarios with no data in controlled studies, this was allowed if the amount of retrospective data was considered significant and scientifically reliable); recommendations based on data obtained from case reports were not allowed. (d) Evidence was collected from studies including primary SjS patients fulfilling the 2002/2016 criteria (SjS-2002).[15 16] When no evidence was available, evidence from studies including associated SjS, patients fulfilling previous sets of criteria or those including a mix of autoimmune and non-autoimmune aetiologies was considered and extrapolated (online supplementary table S1). (e) The balance between efficacy and side effects was evaluated agent by agent. (f) Although recommendations are primarily supported by the evidence reported in patients with primary SjS, the advice on topical and systemic management contained in these guidelines may be applicable to patients with associated (or secondary) SjS.

Systematic literature review

A previous systematic literature review (SLR) reported by the convenor in 2010[7] served to provide SC members with a background to initiate discussions and propose research questions for the SLR focused on the therapeutic management of SjS. On the basis of the research questions, PBZ and SR carried out the SLR between January 1986 and December 2017, with the supervision of the convenor and the methodologists. Summary-of-findings (SoF) tables were generated and levels of evidence (LoE) were determined according to the study design, using the Oxford CEBM standards[17] (online supplementary table S1). The SoFs of the SLR were presented to the SC, whose members formulated a first draft of recommendations based on this information, using electronic and cloud-based working strategies to review the literature search, making comments and maintaining open communication for electronic discussion and amendments. The SLR informing the SC and TF and a detailed description of the methods is published separately. [18] (

Task Force

The TF (online supplementary appendix 1) included 77 specialists in rheumatology, internal medicine, oral health, ophthalmology, gynaecology, dermatology and epidemiology, statisticians, general practitioners, nurses and patient representatives from 30 countries of the five continents (Argentina, Australia, Brazil, Canada, China, Denmark, Egypt, Finland, France, Germany, Greece, Hungary, India, Israel, Italy, Japan, Mexico, Norway, Poland, Portugal, Slovenia, South Korea, Spain, Sweden, Switzerland, the Netherlands, Turkey, the UK and the USA). All TF members declared all potential conflicts of interest. After presentation of the SLR results and the SC proposals to the TF in the first face-to-face meeting, the TF was split into nine breakout working groups (see online supplementary text). Each group proposed draft language and diagnostic/therapeutic algorithms for the respective recommendations to the whole TF. Safety aspects were addressed in each breakout group. Formal economic analyses were not performed, but cost aspects were considered throughout the process. Representatives of each breakout group reported the results of the respective deliberations and presented proposals for the wording of individual recommendations to the whole TF for further discussion and refinement in the second face-to-face meeting.

Consensus findings

After the second meeting, a web-based Delphi procedure was carried out using online voting.[19] The Delphi procedure was designed by MR-C and PB-Z, and developed, managed and analysed by BK using Google Forms; all clinical experts in SjS included in the TF were invited to participate in the Delphi procedure. For an overarching principle or recommendation to be accepted for the final document, TF members were asked to grade for priority according to the level of importance in the daily therapeutic management of SjS (from 1 as unimportant, no priority, no relevance to 5 as very important, a most relevant point, first-order priority); a specific section allowed the inclusion of comments suggested to accompany individual items. Recommendations scoring ≥4 ('important') by >80% of participants were accepted; if this result was not achieved, the respective text was amended and subjected to a second electronic ballot. The approved recommendations were subjected to

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Table 1 Overarching (A–C) and specific (1–12) recommendations

	LoE	GoR	Vote (%)	LoA (0–10)
A.Patients with SjS should be managed at, or in close collaboration with, centres of expertise following a multidisciplinary approach	NA	NA	90	9.2
B.The first therapeutic approach for dryness should be symptomatic relief using topical therapies	NA	NA	93	8.9
C.Systemic therapies may be considered for the treatment of active systemic disease	NA	NA	90	9.1
1.Baseline evaluation of salivary gland function is recommended before starting treatment for oral dryness	5	D	81	8.7
2.The preferred first therapeutic approach for oral dryness according to salivary gland function may be:	1a/*1b	B	88	8.7
2.1. Non-pharmacological stimulation for mild dysfunction;				
2.2. Pharmacological stimulation* for moderate dysfunction;				
2.3. Saliva substitution for severe dysfunction				
3.The first-line therapeutic approach to ocular dryness includes the use of artificial tears and ocular gels/ointments	1a	B	98	9.5
4.Refractory/severe ocular dryness may be managed using topical immunosuppressive-containing drops* and autologous serum eye drops	1a/*1b	B/D	94	9.1
5.Concomitant diseases should be evaluated in patients presenting with fatigue/pain, whose severity should be scored using specific tools	5	D	93	9.0
6.Consider analgesics or other pain-modifying agents for musculoskeletal pain, considering the balance between potential benefits and side-effects	4	C	89	8.9
7.Treatment of systemic disease should be tailored to organ-specific severity using the ESSDAI definitions	4	C	89	9.0
8.Glucocorticoids should be used at the minimum dose and length of time necessary to control active systemic disease	4	C	85	9.6
9.Immunosuppressive agents should be mainly used as GC-sparing agents, with no evidence supporting the choice of one agent over another	4	C	82	8.9
10.B-cell targeted therapies may be considered in patients with severe, refractory systemic disease	1b	B	98	8.6
11.The systemic organ-specific therapeutic approach may follow, as a general rule, the sequential (or combined) use of GCs, immunosuppressive agents and biologics	5	D	98	8.6
12.Treatment of B-cell lymphoma should be individualised according to the specific histological subtype and disease stage	4	C	88	9.7

LoE and GoR according to the Oxford Centre for Evidence-based Medicine—LoE (March 2009). Vote (%): % of participants scoring the recommendation as at least 'important' (score of ≥4 on 5-point scale). LoA: mean score (scale of '0' as no agreement, '10' full agreement).
ESSDAI, EULAR Sjögren's syndrome disease activity index; EULAR, European League Against Rheumatism; GC, glucocorticoid; GoR, grade of recommendation; LoA, levels of agreement; LoE, levels of evidence; NA, not applicable.

an anonymous electronic vote on the levels of agreement (LoA). Each recommendation was adjudicated on a scale of 0–10 (0, no agreement; 10, full agreement).

The draft of the manuscript was written by MR-C and PB-Z and was sent to TF members for comment and, after incorporating these comments, to the EULAR Executive Committee for review and approval. Final remarks were obtained from members of the TF and the Executive Committee and addressed in the manuscript (all modifications required approval by the SC), which was then submitted with the final approval of the EULAR Executive Committee after being presented in the EULAR 2019 meeting.[20]

RESULTS

General recommendations

As in other EULAR recommendations, the TF endorsed the presentation of general principles for the management of patients with SjS as overarching, general consensus-based recommendations, since the contents were so generic that there was no requirement to base them on the SLR (table 1).

Patients with SjS should be managed at, or in close collaboration with, centres of expertise using a multidisciplinary approach(*LoE na; LoA 9.2*)

SjS may be a serious systemic disease, not only due to the heavy impact on the health-related quality of live (HRQoL) of the predominant symptoms (the triplet of dryness, fatigue and pain), but also due to the involvement of internal organs (systemic involvement) and the excess mortality caused by cancer (lymphoma). The low frequency of SjS in the general population, combined with a heterogeneous glandular/systemic clinical expression, makes it difficult to ensure a standardised depth of expertise in managing the disease in non-specialised clinical settings. Therefore, we recommend organising SjS management in and around centres of expertise, including professionals with solid clinical experience in assessing patients with SAD. Assessment of SjS patients requires expert guidance, not only to confirm the diagnosis by ruling out non-autoimmune aetiologies (especially for sicca symptoms), but also to evaluate the extent of organs damaged and to design a specific personalised follow-up according to the clinical and biological patient phenotype at diagnosis.[21] A multidisciplinary approach involving various health professionals is essential, with a central role for specialists in autoimmune diseases, who should act as the coordinator of diagnostic and therapeutic healthcare processes, based on a shared-decision policy between the patient and the specialist. The involvement of primary care physicians and other health professionals is highly recommended in the management of SjS patients.

The first therapeutic approach to dryness should be symptomatic relief using topical therapies (*LoE na; LoA 8.9*)

More than 95% of SjS patients present with sicca symptoms,[22] which have a significant impact on the HRQoL.[23–25] Studies that have evaluated the natural history of glandular function in primary SjS (summarised by Haldorsen *et al*)[26] report that, except in early stages of the disease, dysfunction may remain stable for long periods of time (up to 12 years) and have a chronic course, and no study has demonstrated that any therapeutic intervention can reverse glandular dysfunction and, therefore, can cure sicca symptoms. Since the complete disappearance of dryness, which is the desired target for all patients,

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Table 2 Glossary and definitions

Term	Definition	Examples
1.Nomenclature of therapies 1.1. Topical therapies 1.2. Systemic therapies	1.1. Interventions directly applied to the mucosal surfaces involved 1.2. Drugs administered orally or intravenously for systemic disease	1.1. Saliva substitutes, ocular tears 1.2. Antimalarials, glucocorticoids, immunosuppressive agents, intravenous immunoglobulins, biologics
2.Disease activity terms 2.1. Systemic disease 2.2. Active systemic disease 2.3. Severe systemic disease 2.4. Refractory systemic disease 2.5. Therapeutic response	2.1. Disease involvement that affects or has affected any of the organs/systems included in the clinESSDAI score 2.2. Patients with clinESSDAI score ≥1. 2.3. Patients with ESSDAI score >14, or high activity in any of the ESSDAI domains with a definition of high activity 2.4. Systemic manifestation/s refractory to SOC. 2.5. Decrease of ≥3 points in the global ESSDAI score	2.1. All ESSDAI domains except biological domain 2.2. Systemic activity is classified as low if ESSDAI is 1–4 (if not only due to biological domain), moderate between 5–13 and high ≥14. 2.3. Lymphadenopathy and lymphoma, articular, cutaneous, pulmonary, renal, muscular central and peripheral neurological and haematological domains. 2.4. Due to the diversity of systemic manifestations, SOC (first-line therapeutic approach) has been defined for each systemic manifestation (figure 3) –
3.Ocular dryness 3.1. Refractory 3.2. Severe	3.1. Refractory ocular dryness is defined as not improvement after using the best-available SOC and ruling out other SjS-unrelated processes, 3.2. Severity should be defined after a specific ophthalmological evaluation of corneal damage by ocular scores:	3.1. SOC defined as the maximum use of artificial tears and ointments according to the previous recommendation 3.2. Measurement of the OSS and OSDI ocular scores
4.Recommended instruments of measure 4.1. Salivary gland function 4.2. Corneal damage 4.3. Fatigue 4.4. Pain 4.5. Quality of life 4.6. Systemic disease	4.1. UWSF, SWSF 4.2. OSS, OSDI 4.3. ESSPRI domains, ProFAD 4.4. ESSPRI domains, BPI 4.5. ESSPRI 4.6. ESSDAI, clinESSDAI	
5.Potential life-threatening systemic manifestations	5.1. Cutaneous domain 5.2. Pulmonary domain 5.3. Renal domain 5.4. Muscular domain 5.5. Peripheral nerve system domain 5.6. CNS domain 5.7. Haematological domain	5.1. Diffuse vasculitis with ulcers 5.2. ILD with NHYA III/IV 5.3. Renal failure; rapidly-progressive glomerulonephritis; hypokalaemic paralysis 5.4. Muscular involvement with severe weakness 5.5. Neuropathy (including ganglionopathy and polyradiculopathies) with severe motor deficit/ataxia; cryoglobulinemic-related multineuritis 5.6. Demyelinating disease with motor deficit; cerebral vasculitis presenting with focal deficit; myelitis; meningoencephalitis 5.7. Severe haemolytic anaemia (<80 g/dL, <50 x109/L); severe autoimmune thrombocytopenia (<50 000/mm3)

BPI, brief pain inventory; CHB, congenital heart block; CIDP, chronic inflammatory demyelinating polyradiculopathy; CNS, central nervous system; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; EULAR, European League Against Rheumatism; G-CSF, granulocyte colony-stimulating factor; ILD, interstitial lung disease; KCS, keratoconjunctivitis sicca; LIP, lymphoid interstitial pneumonitis; MMF, mycophenolate mofetil; MP, methylpredisolone; MS, multiple sclerosis; NAC, N-acetylcysteine; NHYA, New York Heart Association; NMOSD, neuromyelitis optica spectrum disorder; NSIP, non-specific interstitial pneumonitis; OP, organising pneumonitis; OSDI, Ocular Surface Disease Index; OSS, Ocular Staining Score; PN, peripheral neuropathy; ROR, retinoic acid-related orphan receptor; RTX, rituximab; SjS, Sjögren syndrome; SOC, standard of care; STAT, signal transducer and activator of transcriptionm; SWSF, stimulated whole salivary flows; TOR, mammalian target of rapamycin; UIP, usual interstitial pneumonitis; UWSF, unstimulated whole salivary flows.

is at present unreachable, the TF recommends exploring the use of other, more realistic outcomes, such as the minimal clinically-important improvement or the patient-acceptable symptom state, following the corresponding ESSPRI definitions,[13] always closely aligned with patient education, including coping strategies. The chronic course of SjS means a daily, long-term use of therapies and, in this scenario, it is reasonable to recommend the use of therapies with a minimum of (or at least tolerable and reversible) side effects. This is overwhelmingly fulfilled by topical therapies (see definition in table 2). Various studies and Cochrane SLRs support the daily use of topical therapies for the symptomatic relief of dryness, with a significant improvement in HRQoL without significant side effects.[7 27 28] These therapies should be immediately initiated after objective confirmation of glandular dysfunction.

Systemic therapies may be considered for the treatment of active systemic disease (*LoE na; LoA 9.1*)

Systemic disease is a key prognostic determinant of SjS and is linked to autoimmune-mediated organ/s dysfunction that may eventually become irreversible. The use of systemic immunomodulatory/immunosuppressive therapies (glucocorticoids (GCs), antimalarials, immunosuppressive agents, intravenous immunoglobulins and biologics) should be restricted to patients with active systemic disease (see definition in table 2) but only after a careful organ-by-organ evaluation of both severity and organ damage, since not all patients with active systemic disease will necessarily require systemic therapy (this was why the original wording using 'should be' was changed to 'may be'). As a general rule, the management of systemic features in SjS should follow a schedule consisting of a two-stage sequential regimen as used in other SAD, including a first intensive immunosuppressive approach targeted to restore organ function (induction of remission) as soon as possible, followed by a second therapeutic course aimed at maintaining the initial therapeutic response (maintenance of remission). Unfortunately, there are no available data in patients with SjS to support specific recommendations on the need for/duration of induction and maintenance therapies, which should therefore be decided on case-by-case.

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Specific recommendations

The 12 specific recommendations form a logical sequence, starting with the management of the central triplet of symptoms (dryness, fatigue and pain) followed by the management of systemic, extraglandular disease (table 1).

Baseline evaluation of salivary gland function is recommended before starting treatment for oral dryness (*LoE 5, LoA 8.7*)

The therapeutic approach to oral dryness should be driven by the baseline measurement of salivary glandular function, and not by the patient's subjective feelings, since environmental and personal stressing factors may influence the subjective feeling of dryness,[29] which often does not match with the objective measurement of glandular function. We recommend the baseline evaluation of salivary glandular function by measuring whole salivary flows before starting therapeutic interventions, always ruling out SjS-unrelated conditions (ie, candidiasis, burning mouth syndrome); salivary scintigraphy may also be considered.[30] This item elicited significant discussions about the specific tests for measuring glandular function (unstimulated whole salivary flows and stimulated whole salivary flows (SWSF), and salivary scintigraphy), especially the use of SWSF and salivary scintigraphy, which were considered as complicated tests in daily practice by several TF members, and not always available in all clinical settings.

The preferred first therapeutic approach for oral dryness according to salivary gland function may be: Non-pharmacological stimulation for mild dysfunction; pharmacological stimulation for moderate dysfunction*; saliva substitution for severe dysfunction (*LoE 1a/*1b, LoA 8.7*)

On the basis of the results obtained in the measurement of salivary gland function, the therapeutic approach to oral dryness may be initiated based on two mechanisms: salivary gland stimulation (non-pharmacological or pharmacological) or saliva substitution (figure 1).[31]

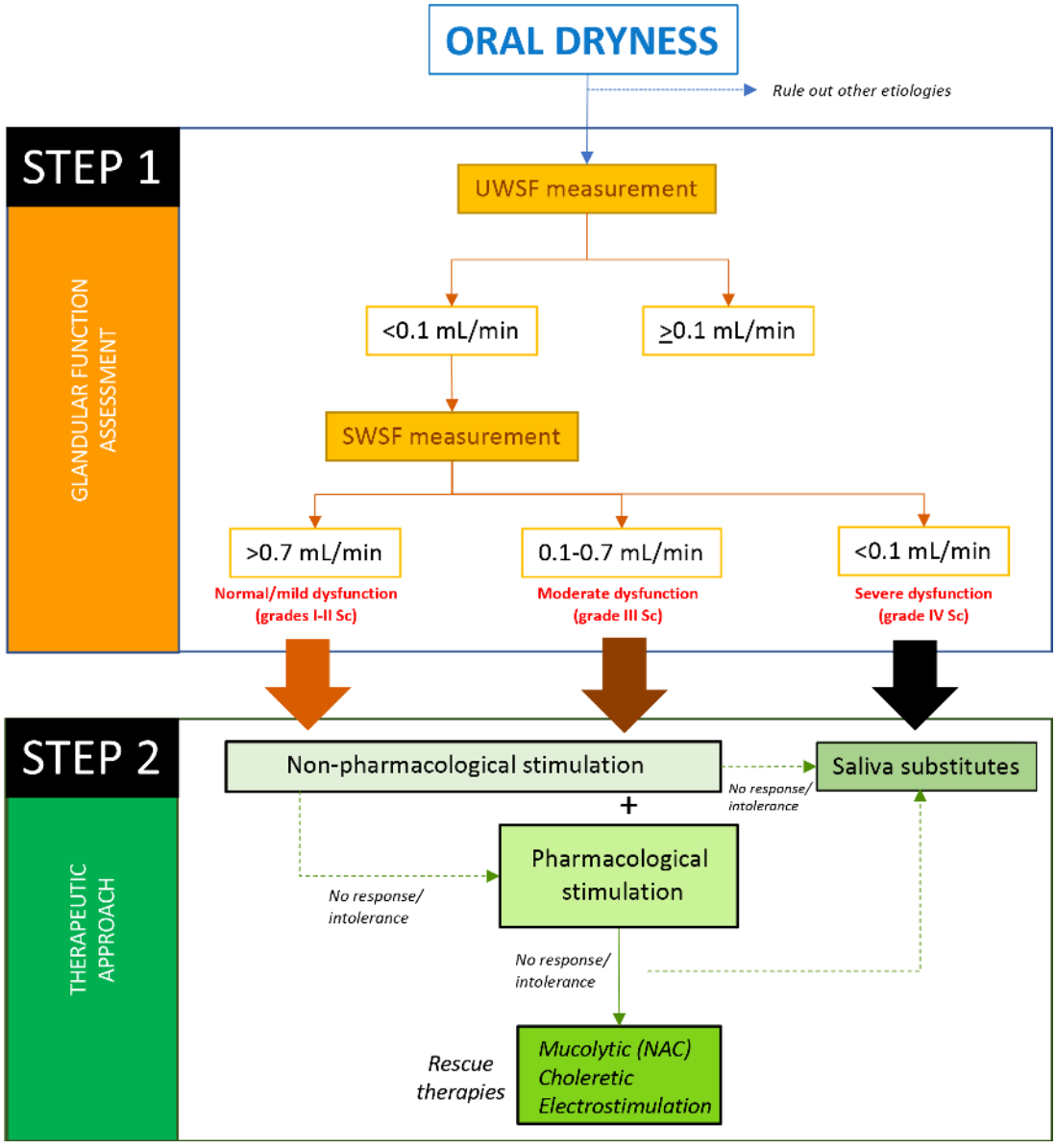

Figure 1 Algorithm of glandular function assessment and therapeutic approach in patients with primary SjS presenting with oral dryness. SjS, Sjögren syndrome; SWSF, stimulated whole salivary flows; UWSF, unstimulated whole salivary flows.

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Non-pharmacological stimulation

In patients with mild glandular dysfunction, we recommend non-pharmacological glandular stimulation as the preferred first-line therapeutic approach, using gustatory stimulants (sugar-free acidic candies, lozenges, xylitol) and/or mechanical stimulants (sugar-free chewing gum) since, in these patients, glandular function can be stimulated (figure 1). With no evidence available for pSjS-2002 patients, evidence was extrapolated from a Cochrane SLR[27] focussed on the therapeutic management of oral dryness; the authors concluded that all non-pharmacological interventions evaluated relieve subjective symptoms to some, unquantified degree, without strong evidence that any intervention was more effective than another, although no study evaluated the therapeutic response according to the degree of salivary gland dysfunction.[27]

Pharmacological stimulation

In patients with moderate glandular dysfunction, pharmacological stimulation with muscarinic agonists may be considered. Two drugs (pilocarpine and cevimeline) are licensed for the treatment of oral dryness, although only pilocarpine is licensed worldwide. The three pivotal randomised controlled trials (RCTs) included both primary and associated SjS patients fulfilling the 1993 criteria, and found significant improvements in visual analogue scale (VAS) dry mouth and salivary flow rates, with a high frequency of adverse events.[7] The available evidence in pSjS-2002 patients is limited to one small prospective study using pilocarpine that found improvement in subjective but not objective oral outcomes,[32] and a second study with no detailed information about overall efficacy and safety.[33] A third retrospective study which compares pilocarpine and cevimeline, only focussed on the safety profile,[34] and reported a better tolerance profile for cevimeline. The evidence is too limited to make a strong recommendation for pSjS-2002 patients (the best level of evidence should be extrapolated from RCTs including patients fulfilling the former 1993 criteria). For this reason, and together with the unfavourable safety profile of these drugs, we recommend offering a trial of muscarinic agonists to patients with moderate glandular dysfunction (or in those with mild dysfunction who are refractory or who do not wish to use non-pharmacological stimulation) (LoE 1b, GoR B) (figure 1). To reduce the main side effect (excess sweating), and based on clinical practice, some TF experts recommended increasing the dose progressively up to 15 to 20 mg/day when possible. In patients who are intolerant or non-responders to muscarinic agents, some choleretic (anetholtrithione) or mucolytic (bromhexine, N-acetylcysteine) agents used as secretagogues in SjS since the 1980s may be considered as rescue therapies due to their good safety profile in the absence of alternative therapeutic options, and taking into account the limitations of the study design and the marginal benefits reported by most studies.[7] According to the SLR results, for the treatment of oral dryness we do not recommend the use of hydroxychloroquine (no placebo-differences for subjective and objective oral outcomes in the pivotal RCT), oral GCs, immunosuppressive agents (overwhelmingly-negative results with excess side effects) or rituximab (no placebo-differences for subjective and objective oral outcomes in the two pivotal RCT and one meta-analysis)

Saliva substitution

Saliva substitution should be considered the preferred therapeutic approach to alleviate symptoms in patients with no residual glandular function (severe glandular dysfunction), in whom salivary glands cannot be stimulated, either by pharmacological or non-pharmacological interventions (figure 1). The ideal preparation will have a neutral pH and contain fluoride and other electrolytes, mimicking the composition of natural saliva; saliva substitutes are available commercially in the form of oral sprays, gels and rinses.[10] Only one prospective study evaluated pSjS-2002 patients[35] and found no statistically-significant placebo-differences for the primary outcome, although significant improvements were reported in some subjective oral outcomes, with no side effects reported. Evidence can be extrapolated from a Cochrane SLR that evaluated the effectiveness of topical treatments for any-cause dry mouth; the review found no superiority for any therapeutic option.[27] In spite of the limited evidence available, we recommend their use in the target population because, in the experience of TF members, patients often report increased oral comfort without significant side effects.[10] Oral gel-like formulations may be useful in patients with an acceptable salivary flow output, particularly when they complain about nocturnal oral dryness, although these patients often have a poor tolerance to saliva substitutes due to the sticky feeling caused by their application, which may be reduced by diluting the saliva substitute. Pretherapeutic evaluation of salivary function may also aid the choice of a specific formulation of saliva substitutes (gel, saliva substitute—diluted or not,mouth rinses), with less thick/dense preparations being preferred for patients with a better-preserved glandular function.[36] The preferred first-line use of saliva substitutes in patients with no salivary output elicited an intense debate within the TF, probably due to the apparent paradox of using a topical therapy in patients with severe glandular involvement. Several TF members expressed a dissenting view, stating that saliva substitutes should be used in all patients with oral dryness, irrespective of glandular function. Whether or not a saliva substitute is used, a neutral pH sodium fluoride gel should be prescribed to all patients with severe salivary dysfunction to prevent rampant caries.

The first-line therapeutic approach to ocular dryness includes artificial tears and ocular gels/ointments (*LoE 1a, LoA 9.5*)

The first line of therapy for ocular dryness should be volume replacement and lubrication using artificial tears (AT) and ocular gels, whose main ingredients are lubricants with a polymeric base or viscosity agent (methylcellulose, hyaluronate) with the aim of adding volume to the tear lake, increasing the time the AT remain on the ocular surface, and cushioning the ocular surface to reduce friction between lid and globe.[37] All SjS studies testing AT (only one in pSjS-2002 patients) found significant improvements for both subjective and objective ocular outcomes, while a recent Cochrane review on the use of AT for dry eye syndrome showed that they are safe and effective.[28] We recommend that all SjS patients presenting with ocular dryness and/or abnormal ocular tests should use AT containing methylcellulose or hyaluronate at least twice daily, with the frequency increased to as often as hourly, as indicated by symptoms and/or objective signs. The use of preservative-free formulations of AT is mainly recommended in patients requiring four or more applications per day. Ophthalmic ointments are thicker than AT and may be used to provide symptom control overnight; they are typically used before bedtime because they produce blurred vision and their use should be followed by morning lid hygiene to prevent blepharitis.[37]

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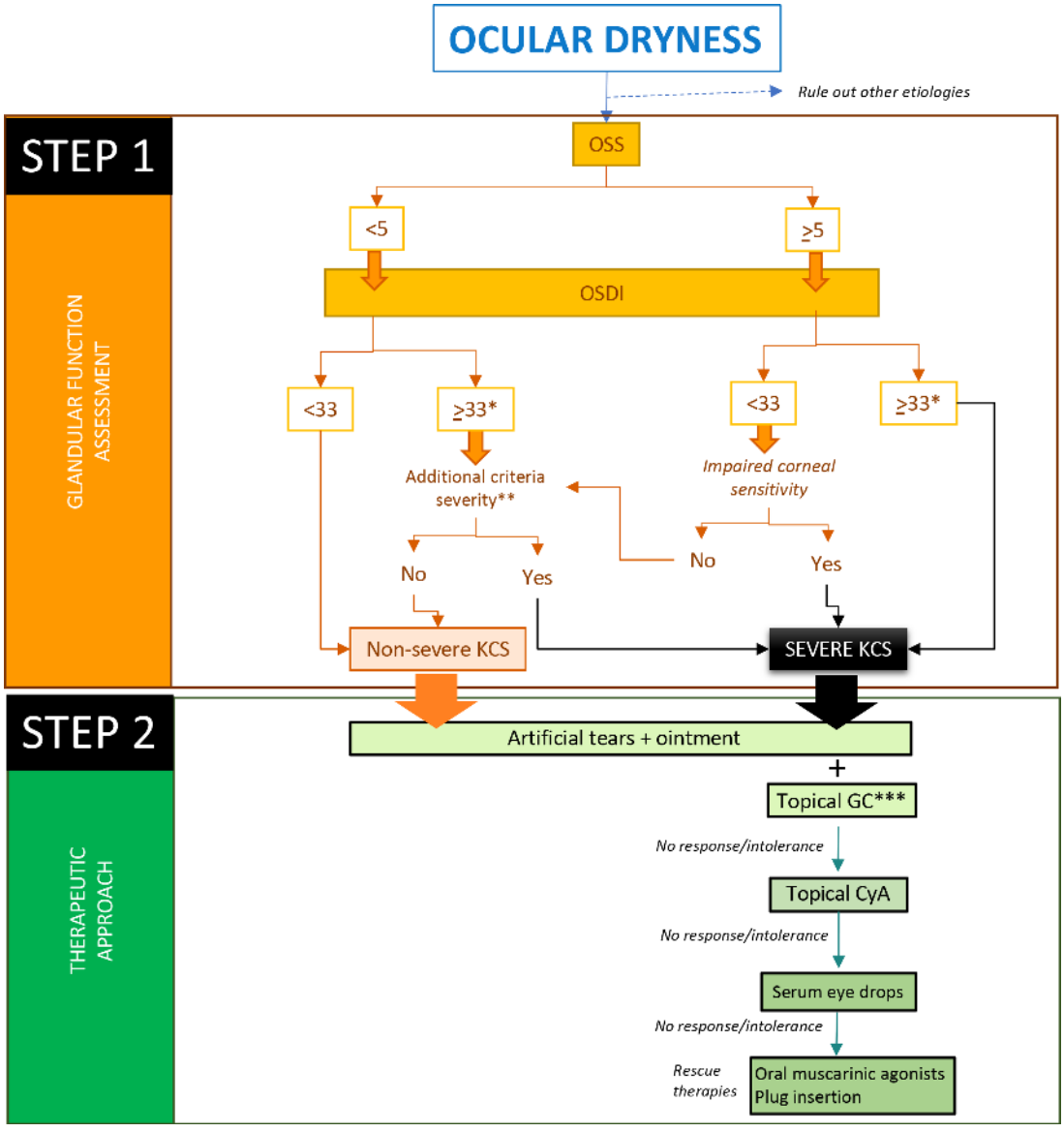

Figure 2 Algorithm of glandular function assessment and therapeutic approach in patients with primary SjS presenting with ocular dryness. *Consider neuropathic pain if OSS≤1. **Additional criteria for severity: (1) impaired visual function (photophobia, visual acuity modification or low contrast sensitivity); (2) blepharospasm (secondary to ocular inflammation); (3) severe meibomian gland disease or eyelid inflammation. ***For short-term indications (2–4 weeks). CyA, ciclosporin A; GC, glucocorticoid; OSS, ocular staining score (Whitcher[107] JP, *et al*. Am J Ophthalmol. 2010;149:405–15). OSDI, ocular surface disease index (adapted from Baudouin C,[108] *et al*. Br J Ophthalmol 2014;98:1168–1176); SjS, Sjögren syndrome.

Refractory/severe ocular dryness may be managed using topical immunosuppressive-containing drops* and serum eye drops (*LoE 1a/*1b, LoA 9.1*)

Patients with refractory or severe ocular dryness should be managed by an ophthalmologist with substantial experience in corneal disease wherever possible. Refractory ocular dryness is defined as patients who do not improve after using the best-available standard of care (SOC) (defined as the maximum use of AT and ointments according to the previous recommendation) after ruling out other SjS-unrelated ocular processes (ie, blepharitis), while severity should be defined according to the results obtained in a specific ophthalmological evaluation of corneal damage by measuring the OSS, together with patient symptoms as assessed by the Ocular Surface Disease Index (figure 2).

Topical NSAIDs/corticosteroids

Topical ocular non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids may be prescribed by ophthalmologists as a short-term therapeutic approach (maximum 2–4 weeks), as adverse events may occur with continued use of topical NSAIDs (corneal–scleral melts, perforation, ulceration and severe keratopathy) or topical corticosteroids (infections, increased intraocular pressure and worsening/development of cataracts).[37] Evidence in pSjS-2002 patients is limited to one small case-control study[38] using topical fluorometholone which found no significant differences in comparison with topical ocular ciclosporin A (CyA).

Topical CyA

In December 2002, an ophthalmic formulation containing 0.05% CyA was approved by the Food and Drug Administration to treat dry eye disease in the USA based on the results of two RCTs including patients with keratoconjunctivitis sicca (SjS patients were included in variable proportions).[7] There are no specific RCTs carried out in pSjS-2002,[39 40] and only one recent case-control study, which reported no significant differences

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between groups in comparison with topical fluorometholone, with a higher frequency of moderate-to-severe transient burning sensation in patients receiving CyA.[38] Ophthalmologists may consider the use of ocular CyA drops in patients with refractory or severe ocular dryness requiring repeated courses of glucocorticoid tear drops. The promising results of a recent small trial using tacrolimus tear drops[41] required further confirmation in large trials.

Serum tear drops

In SjS patients, the role of autologous or allogenic serum has been tested in small uncontrolled studies showing inconsistent benefits (no improvement in all objective ocular outcomes evaluated). A recent Cochrane SLR on the use of serum tear drops for dry eye syndrome[42] has confirmed inconsistencies in their possible benefits both for symptoms and objective measures, with no evidence of an effect after 2 weeks of treatment. Only one study has been carried out in pSjS-2002 patients, which showed significant improvement in some ocular outcomes.[43] The difficulties in preparation, the need to refrigerate the drops, and the potential risk of contamination should be taken into account.[37 44] The TF recommended that serum tear drops may be considered in patients who are non-responders or intolerant to topical CyA tear drops.

Rescue therapies

Other therapeutic interventions may be considered after failure of the above-mentioned therapies, including topical and systemic therapies. A recent Cochrane SLR reviewing the use of plugs for dry eye syndrome[45] found that the evidence was very limited, and concluded that improvements in subjective and objective ocular outcomes were inconclusive. Two studies have been carried out in primary-2002 SjS patients: the first found no significant differences between groups (insertion of plugs vs AT),[46] and the second reported improvement in only two of four ocular outcomes evaluated.[47] With respect to systemic therapies, oral muscarinic agonists may be considered on the basis of the improvement of subjective (not objective) ocular outcomes.[7] According to the SLR results, for the treatment of ocular dryness we do not recommend the use of hydroxychloroquine (no placebo-differences for subjective and objective ocular outcomes in the pivotal RCT), immunosuppressive agents (overwhelmingly negative results with excess side effects) or rituximab (no placebo-differences for subjective and objective oral outcomes in the two pivotal RCT and one meta-analysis).

In summary, although patients with refractory/severe ocular dryness may require a more intensive ophthalmological follow-up and, probably, more complex therapies, including immunosuppressive-based tear drops (topical corticosteroids or CyA) and serum tear drops, the low level of current evidence for the use of these complex ophthalmological therapies in primary SjS-2002 patients do not permit the TF to establish a strong preference among the options. The expertise of the ophthalmologist and the specific characteristics of the patient will drive both the preferred first-line therapy and the sequential use of the therapeutic interventions.

Concomitant diseases should be evaluated in patients presenting with fatigue/pain, whose severity should be scored using specific tools (*LoE 5, LoA 9.0*)

Patients with primary SjS often present with general symptoms, of which most frequent are non-inflammatory joint/muscle pain and fatigue/weakness, which may have a much greater impact on the HRQoL than sicca features, as reported in cross-sectional studies.[23–25] Unfortunately, these symptoms are very unspecific and could be related to a wide range of concomitant pathologies (osteoarthritis, hypothyroidism, hypocortisolism, vitamin deficiencies, depression, neoplasia) and even to some systemic complications of systemic SjS (arthritis, anaemia, hypokalaemia, osteomalacia, lymphoma, small-fibre neuropathy). A specific comment is needed on the association between SjS and some somatic functional syndromes such as chronic fatigue syndrome and fibromyalgia, whose peak of incidence occurs in the same population subset as SjS (middle-aged women).[21] No studies have confirmed a solid aetiopathogenic autoimmune link between SjS and chronic fatigue syndrome/fibromyalgia[48] beyond the evident epidemiological overlap. Since the association of these somatic syndromes could heavily influence both the patient and physician global health status evaluation, we recommend searching for these syndromes using standardised recommendations,[49] and measuring the severity of pain and fatigue using specific scales such as the corresponding ESSPRI domains, the Profile of Fatigue (for measuring fatigue) and the Brief Pain Inventory (for measuring pain).[50] SjS patients may describe various kinds of pain and fatigue, and the use of both general and SjS-specific questionnaires will permit not only a standardised measurement of their potential impact on HRQoL, but consideration of their influence when specific therapeutic interventions are initiated.[10 51]

Consider analgesics or other pain-modifying agents for musculoskeletal pain, taking into account the balance between potential benefits and side-effects (*LoE 4, LoA 8.9*)

With respect to SjS-related musculoskeletal pain, a clear pretherapeutic differentiation must be made clinically between joint pain (arthralgia) and joint inflammation (arthritis, tenosynovitis).[52] The ESSDAI score classifies arthralgia in the hands, wrists, ankles and feet accompanied by morning stiffness (>30 min) as low articular activity level, always ruling out concomitant osteoarthritis. Arthritis is clinically diagnosed on the basis of objective inflammation of ≥1 joints (heat, redness and swelling in the physical examination of the affected joint) supported by ultrasound studies when in doubt, and the ESSDAI score classifies the severity of arthritis according to the number of joints involved (moderate ≤5 joints, high >5).[12] The therapeutic management of arthritis is included in the systemic recommendations. (a) In patients presenting with acute musculoskeletal pain, consider acetaminophen or NSAIDs for symptomatic relief, always for less than 7–10 consecutive days at full dosage and considering the side effects and underlying comorbid diseases. In real life, a large retrospective study in 188 primary 2002 SjS patients with joint involvement reported that nearly one third had a rapid clinical response to the short-term use of analgesics/NSAIDs.[53] Topical formulations of NSAIDs (topical diclofenac or ketoprofen) may be effective for local pain with fewer side effects,[54] but there is no available evidence in SjS patients.[55] (b) In patients with frequent episodes of acute musculoskeletal pain, the use of hydroxychloroquine has been proposed based on its comparable use in other SAD such as systemic lupus erythematosus (SLE). Although uncontrolled studies have reported improvement in joint pain, the pivotal RCT failed to demonstrate that hydroxychloroquine improved pain after 24 weeks of treatment in comparison with placebo, although a statistical trend was reported (p values between 0.06 and 0.10) at 12, 24 and 48 weeks).[56] Taking this positive trend, the lack of reported cases of retinal toxicity or severe adverse events, and the lack of pharmaceutical

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alternatives with a similar indication/safety profile, the TF members agreed to consider the use of hydroxychloroquine in some patients with frequent episodes of articular pain. In real life, the study by Fauchais *et al*[53] reported the use of hydroxychloroquine in more than half the patients presenting with joint involvement. With respect to the use of biological agents to treat these symptoms, the data from the two pivotal RCTs[57 58] on the effect of rituximab on pain and fatigue reported no significant differences in comparison with placebo for both pain and fatigue VAS (although some differences were found at intermediate evaluation points in the French study), together with no significant placebo-differences in quality-adjusted life-year but with a fivefold greater economic cost,[58] while a recent meta-analysis[59] confirmed no significant differences after combining the results of these trials. In addition, a small RCT using anakinra found no significant reduction in fatigue in its primary endpoint,[60] while the promising results obtained in two small open-label studies (<30 patients) using epratuzumab[61] or abatacept[62] must be confirmed in further large RCTs. Therefore, we consider that the off-label use of biological agents to treat only musculoskeletal pain (even as rescue therapy) is not currently warranted. (c) In patients with chronic, daily non-inflammatory pain, the management must be completely different, avoiding the repeated use of NSAIDs or GCs. The non-pharmacological management of pain should be emphasised, instead of going straight to prescribing medications for the symptoms. Therefore, the first therapeutic step should be to follow the same recommendations as those proposed for general chronic pain, by suggesting that physical activity and aerobic exercise are interventions with few adverse events that may reduce pain severity and improve physical function.[63] In addition, a small case-control study in primary SjS patients showed significant improvement in aerobic capacity, fatigue and ratings of perceived exertion and depression in patients allocated to the exercise group.[64] Antidepressants and anticonvulsants may be considered for chronic musculoskeletal pain, while patients with chronic neuropathic pain may require the use of gabapentin, pregabalin or amitriptyline (paying attention to potential exacerbations of dryness symptoms). Recent epidemiological data confirm that opioids must not be used.[65]

Treatment of systemic disease should be tailored to organ-specific severity using the ESSDAI definitions (*LoE 4, LoA 9.0*)

In non-specialised medical settings, primary SjS is often considered a chronic, non-life-threatening disease that only causes dryness, fatigue and pain. However, systemic involvement has been increasingly recognised as a key part of the disease, with a significant weight in dictating the prognosis and survival in retrospective studies.[66–69] The development of the ESSDAI by the EULAR-SS Task Force Group has provided a helpful, objective instrument to measure systemic involvement in primary SjS that is accepted worldwide. According to overarching principle C, we recommend that the use of systemic therapies (GCs, antimalarials, immunosuppressive agents, intravenous immunoglobulins, biologics) should be restricted to patients with active systemic disease (see definitions in table 2). However, the management of systemic features must be tailored to the specific organ involved and the severity evaluated by the ESSDAI.[69] As an overall rule, systemic therapies may be considered for most patients presenting with at least moderate activity in one clinical domain, or with a global moderate disease activity score (score ≥5). With respect to the definition of the therapeutic response in systemic SjS, the TF recommends using a reduction of ≥3 points in the global ESSDAI score.[70] It should also be considered that some systemic manifestations are not captured by the ESSDAI, including Ro-associated congenital heart block, Raynaud phenomenon, primary pulmonary hypertension, pleuritis, pericarditis, dysautonomia, interstitial cystitis and sensorineuronal hearing loss; these features require specific patient-by-patient management.

GCs should be used at the minimum dose and length of time necessary to control active systemic disease (*LoE 4, LoA 9.6*)

The frequent use of GCs in clinical practice in primary SjS patients[69 71 72] is not supported by reliable scientific evidence, since no controlled study has specifically evaluated their use for systemic disease. Available data come mainly from retrospective studies (online supplementary table S2) and case series/reports, which also highlighted the high rate of GC-related adverse events. We recommend that GCs should be used at the minimum dose and length of time necessary to control active systemic disease, administering pulses of methylprednisolone followed by doses of 0.5 mg/kg/d or lower as induction therapy in severe presentations (table 2), and doses<0.5 mg/kg/d in moderate/less-severe presentations, with a final target of withdrawing GCs in inactive patients as soon as possible or at least trying to target a maintenance dose of 5 mg/daily or less with the aid of GC-sparing immunosuppressive agents (see recommendation 'Synthetic immunosuppressive agents should mainly be used as GC-sparing agents, with no evidence supporting the choice of one agent over another (*LoE 4, LoA 8.9*)'). No available data in SjS patients support specific recommendations on the rate of de-escalation of the GC dose, or when a GC-sparing agent should be added, or the length of GC therapy, although we recommend tapering GCs as rapidly as clinically feasible. We recommend to follow the EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases.[73]

Synthetic immunosuppressive agents should mainly be used as GC-sparing agents, with no evidence supporting the choice of one agent over another (*LoE 4, LoA 8.9*)

Based on the potential development of chronic damage in patients with uncontrolled systemic disease, some patients may require long-term therapy with GCs, especially those with severe organ impairments.[69 71 72] In these patients, the addition of immunosuppressive agents as GC-sparing agents is justified, always weighing the potential benefits and risks. The use of immunosuppressive agents in primary SjS is based on the same level of evidence as that of GCs, since all reported studies (prospective uncontrolled studies, all including less than 50 patients) were principally centred on the efficacy in sicca features and laboratory parameters, but not on the efficacy in systemic disease, with an unacceptable rate of adverse events (ranging between 41% and 100%).[7] The lack of head-to-head studies comparing the efficacy and safety profile of immunosuppressive agents in primary SjS-2002 (leflunomide, methotrexate, azathioprine, mycophenolate, cyclophosphamide) does not permit a recommendation on the use of one agent over another, except when patient characteristics or comorbidities are considered with respect to the safety profile. In addition, there is no information available about the dose, route of administration and length of treatment and we recommend a case-by-case evaluation following similar rules to those reported for other SAD. Although some TF members suggested the use of monotherapy with immunosuppressive agents, there was no final consensus on this option due to the lack of studies demonstrating the efficacy

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of GC-free regimens in SjS, and the fact that more than 95% of reported cases using immunosuppressive agents in primary SjS-2002 received associated GCs (online supplementary table S2). Several immunomodulatory agents have been tested in SS, with marginal benefits or with an unacceptable rate of adverse events and are not recommended.[7]

B-cell targeted therapies may be considered in patients with severe, refractory systemic disease (*LoE 1b, LoA 8.6*)

The emergence of biological therapies in this century has increased the therapeutic armamentarium available for treating severe SjS. These new drugs have the highest level of evidence among all the drugs tested for SjS, not only because have they have been tested in a large number of patients (>1000), but also because most of reported RCTs in primary SjS have tested biologics. Unfortunately, their use in clinical practice is clearly limited by the lack of licensing. B-cell targeted therapies are the most frequently tested biological drugs, and include epratuzumab[61] and belimumab,[74 75] although the most widely studied B-cell target therapy is rituximab.[57 58 76–86]

Studies with available data on the efficacy of rituximab on systemic involvement have included more than 400 patients with primary SjS-2002 (online supplementary table S3), with a predominant use of the regimen of 2 doses of 1 g each administered 15 days apart.[7] Four main systemic outcomes were evaluated at different follow-up times in these studies: the global therapeutic response, organ-specific response, change in the global ESSDAI score and reduction in prednisone use. Uncontrolled studies have reported a global response rate of 60%–100% for systemic features, especially cryoglobulinemic features.[76 77 79 80 86] One small RCT[86] reported a significant reduction in reported extraglandular manifestations and improvement of musculoskeletal features at weeks 12 and 36 (p=0.029) and vasculitis at week 24 (p=0.03). Four studies (two retrospective, one case-control and one prospective) have reported a statistically-significant reduction in the global baseline ESSDAI score (from 9 to 20.3 to 2.5–5.2 after treatment).[77–80 84] In the two pivotal RCTs, Devauchelle *et al* found no differences in the mean ESSDAI improvement,[57] while Bowman *et al*[58] reported statistically-significant placebo differences at week 36 (p=0.03) and a statistically-significant trend at week 48 (p=0.07) in the log-transformed ESSDAI score. Three retrospective studies have demonstrated a statistically significant reduction in the daily dose of GCs.[76 79 80] In summary, the great majority of studies showed efficacy in at least one of the systemic outcomes analysed (global response, organ-specific response, ESSDAI reduction, prednisone reduction).

The results of the Efficacy and Safety of Belimumab in Subjects with Primary Sjögren's Syndrome open label trial[74] in 30 pSjS-2002 patients treated with belimumab showed a reduction in the mean ESSDAI score from 8.7 to 5.7 at week 28 (p<0.0001), with a decrease of at least 4 points in 40% of cases and improvements in

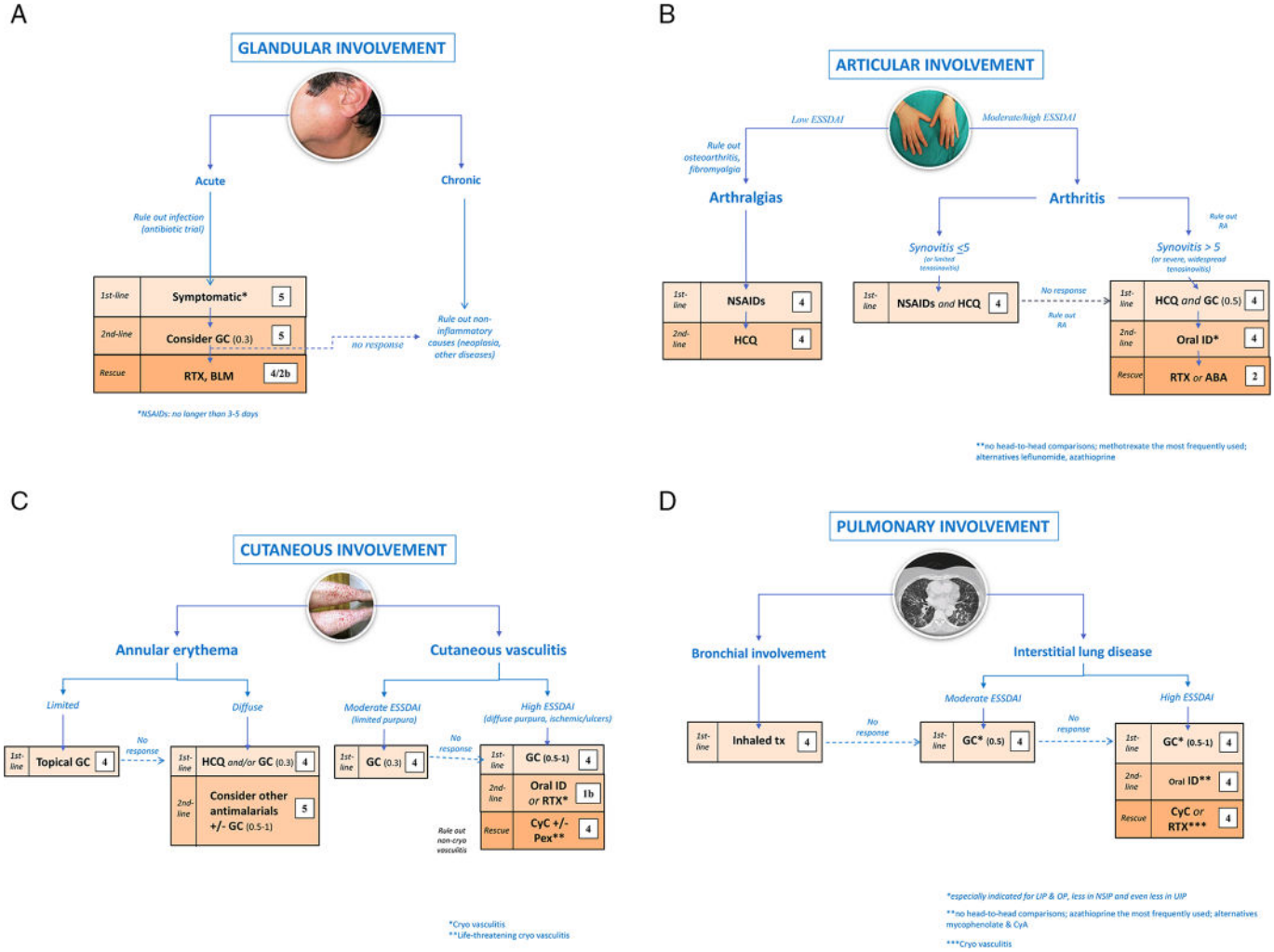

Figure 3 *(Continued)*

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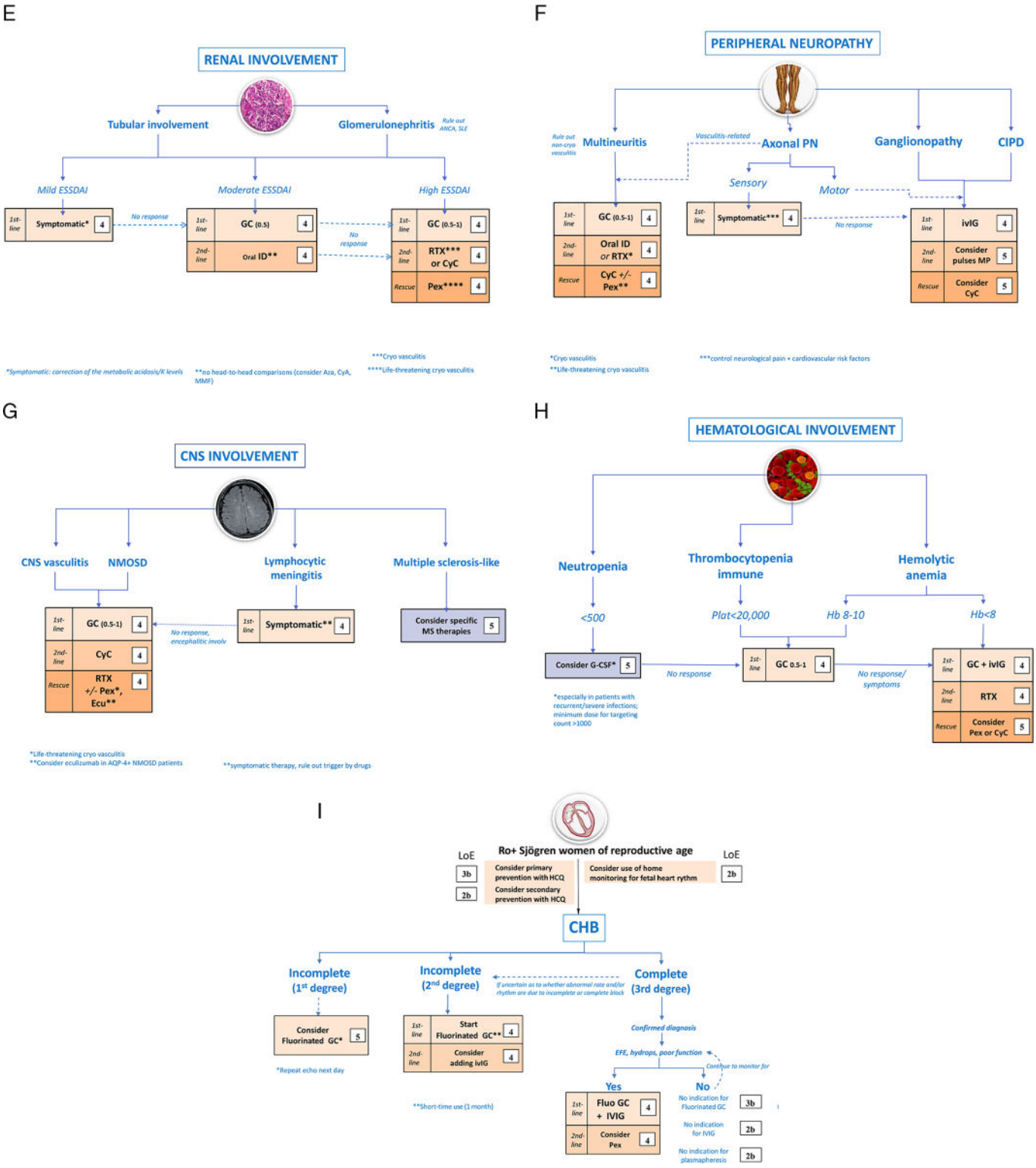

Figure 3 (A to I) Algorithm for the therapeutic approach to patients with primary SjS presenting with organ-specific systemic involvements. NSAIDs: no longer than 7–10 days. HCQ: hydroxychloroquine 200 mg/day. GC (recommended dose in mg/kg/day); short-term course whenever possible; consider methylprednisolone pulses in severe cases. ID: immunosuppressive agents, no head-to-head comparisons. CyC: cyclophosphamide pulses 0.5 g/15 day (maximum six pulses). Rituximab: rituximab 1 g/15 days (x2). BLM: belimumab; 10 mg/kg (0, 2 and 4 weeks and then every 4 weeks). ABA: abatacept 0, 2, 4 weeks and every 4 weeks. IVIg: intravenous immunoglobulins 0.4–2 g/kg 5 days. PEX: plasma exchanges. CyA, ciclosporin A; EULAR, European League Against Rheumatism; ESSDAI, EULAR Sjögren's syndrome disease activity index; GC, glucocorticoid; LoE, levels of evidence; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; SjS, Sjögren syndrome.

parotid swelling in 77% of cases; of five patients previously refractory to rituximab, belimumab was effective in 3 (60%). In a study extension of the 19 patients that completed 1 year of treatment, a significant improvement was maintained.[75] With respect to the safety profile, one severe adverse event was reported (pneumococcal meningitis) after 6 infusions of belimumab.

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After intense discussion among the TF members and balancing the positive results of uncontrolled studies, the weak evidence reported by RCTs, and the fact that the trials were not primarily designed to evaluate the systemic response, we agreed that the use of rituximab may be considered (we changed the original wording of 'should be') in patients with severe, refractory systemic disease, and that the best indication is probably for symptoms linked to cryoglobulinemic-associated vasculitis,[87] with the possible use of belimumab as rescue therapy.

The systemic organ-specific therapeutic approach may, as a general rule, follow the sequential (or combined) use of GCs, immunosuppressive agents and biologics (*LoE 5, LoA 8.6*)

The recommended general sequential use of the three main categories of immunosuppressive agents in SjS is based on a similar approach to that reported for other SAD such as SLE or vasculitis, with no controlled studies supporting this approach in SjS. As a general rule, for most systemic involvements GCs (see recommendation 'GCs should be used at the minimum dose and length of time necessary to control active systemic disease *(LoE4, LoA9.6)*') may be considered the first-line option in patients with active systemic disease, and immunosuppressive agents and biologics as second/third line options to be used in patients intolerant or refractory to GCs, those with severe disease or those in whom long-term GC use is anticipated. In spite of the greater amount of scientific evidence data available for rituximab in comparison with GCs and immunosuppressive agents, the lack of licensing, the lack of controlled studies for systemic disease and the lack of head-to-head comparisons between rituximab and classic immunosuppressants (especially with respect to the safety profile) were issues to be considered. After an intense discussion among the TF members, the TF agreed to merge the two options as second-line therapies (adding a specific note about the use of rituximab as especially recommended for associated cryoglobulinemic vasculitis), always with a careful case-by-case assessment of the use of rituximab in an off-label context, evaluating potential benefits and adverse effects patient-by-patient (table 2), and taking into account the fact that their use will depend on drug availability and national regulations.

Unfortunately, after analysing the available evidence, no controlled data was identified to support a differentiated organ-guided therapeutic approach for systemic SjS, and some TF members recommend no strictly adherence to sequential therapy management, with an individualised therapeutic approach being preferable. However, on the basis of the results, principally from retrospective studies (online supplementary table S2), together with the clinical experience of the TF members, a list of consensus-based algorithms defining SOC and second/third line therapies was proposed for each clinical ESSDAI domain (figure 3A–I); Ro-associated congenital heart block (not included in the ESSDAI) was also included due to its prognostic significance. There was no consensus on the proposal to make recommendations for organ-specific maintenance therapeutic regimens.

Treatment of B-cell lymphoma should be individualised according to the specific histological subtype and disease stage (*LoE 4, LoA 9.7*)

Among the systemic manifestations of SjS, lymphoma is one of the worst complications, with standardised incidence ratios for B-cell lymphoma ranging between 7 and 9 in population-based studies and between 16 and 48 in hospital-based studies.[88] Although the vast majority of cells infiltrating the salivary glands of patients with primary SjS are T cells, the majority of lymphomas reported are of B-cell origin with a ratio between B and T-cell lymphomas of 15:1; three subtypes of B-cell lymphoma account for more than 90% of reported cases in primary SjS: mucosa-associated lymphoid tissue (MALT) lymphoma, other marginal zone lymphomas (MZL) and Diffuse large B cell lymphoma.[88] Following the diagnosis of lymphoma, therapy should be individualised according to the specific histological subtype defined according to the WHO 2016 classification[89] and the corresponding current therapeutic guidelines, with a personalised therapeutic approach driven by the haematologist/oncologist. For primary SjS-2002 patients diagnosed with low grade haematological neoplasia, some clinicians recommend a watchful waiting approach when lymphoma only affects the exocrine glands,[90] especially in the absence of constitutional symptoms, systemic features or B-cell activation biomarkers.[3] The decision to treat low-grade lymphomas or not must be discussed in a multidisciplinary committee, taking into account the fact that they are linked to the disease activity and are the ultimate stage of autoimmune B-cell activation. Moreover, low grade B-cell lymphomas have a potential risk of progression to more aggressive types of lymphoma.[3] In patients with disseminated MALT lymphoma or with concomitant high disease activity, chemotherapy may be considered on a case-by-case basis.[3] For patients with marginal zone lymphomas, small lymphocytic lymphoma (SLL) and lymphoplasmacytic lymphoma (LPL) in early disease stages (in particular, stage I or non-bulky stage II), treatment may include radiotherapy (with or without chemotherapy), although a watch-and-wait strategy could be an alternative to spare the side effects of therapy.[91] For patients with moderate/high grade haematological neoplasia, treatment is based on standard rituximab-based chemotherapy regimens. The benefit of adding rituximab to chemotherapy has been demonstrated in a meta-analysis in patients with follicular lymphomas, mantle cell lymphomas and other indolent lymphomas.[91] Rituximab plus fludarabine or bendamustine (BR) are the recommended first-line therapy for MZL, SLL and LPL; a recent study in 13 patients with pSjS-2002 (77% stage IV) complicated by MZL has reported the efficacy of the BR combination in all 13 cases, with improvement in the other SjS non-lymphomatous manifestations and with a good safety profile.[92]

DISCUSSION

The EULAR recommendations for the management of SjS with topical and systemic therapies management have been developed by a large, multidisciplinary, multiprofessional team. In summary, nine RCTs (only three including 120–130 patients), 18 prospective (all including between 10 and 50 patients) and five case-control studies were selected to support the scientific evidence presented here. This is a small number of studies that is not comparable with rheumatoid arthritis (RA) or with other, more closely-related diseases, such as SLE or systemic vasculitis. Therefore, the evidence accumulated in this century reveals SjS as a true orphan disease from a therapeutic point of view,[59 93] with the absence of any efficacious agent, a situation that is in clear contrast with the significant advances achieved in both basic and clinical research during this period. As a consequence of the limited evidence available, therapeutic decisions in daily practice are often based on a mix of reported expert opinions and personal experience, which may vary widely between countries: therefore, the present recommendations are based on the input of experts from 16 European countries and wide international representation from the other continents. In addition, SjS presents with a wide range of signs and symptoms (not only the key features of dryness, fatigue and pain, but also those derived from organ-specific systemic involvements and lymphoma), with

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a large number of different specialties involved and, therefore, with a wide variety of potential interventions. Methodologically, we have also taken into account the continuous changes in classification criteria since 1986 and, in consequence, the continuous changes in the target population classified as primary SjS. For this reason, we decided, in the Population, Intervention, Comparison, Outcomes and Study design strategy, to focus on the evidence collected from therapeutic studies including pSjS-2002 patients, since these criteria have been used for a longer and more-recent period and because of their similarity with the recent 2016 American College of Rheumatology (ACR)/EULAR criteria.[16]

In SjS, we are very far from the 'disease modification' concept as the mainstay of treatment (as used in other diseases such as RA, a concept that allows the use of the term disease modifying antirheumatic drugs for many drugs that have demonstrated the ability to prevent structural damage progression in RA). A rapid overview of the LoE that support each statement (table 1) shows that all recommendations for managing oral and ocular dryness are principally supported by evidence extrapolated from Cochrane SLRs that evaluated their management in mixed aetiological populations; on the management/prevention of dryness-related complications (oral ulcers, candidiasis, caries/dental complications, ocular infections), the management of dryness other than oral or ocular, or the role of non-therapeutic interventions in dryness, there was a very limited number of studies carried out in 2002 primary SjS patients, and we recommend following published guidelines.[9–11 37 94] With respect to the most frequently used synthetic drugs (GCs and immunosuppressive agents), the available evidence came from isolated uncontrolled studies. The only exceptions were for hydroxychloroquine and rituximab, which were both tested in well-designed RCTs, although there were no statistically-significant differences with respect to placebo for the primary outcome (efficacy in dryness, fatigue and pain). With respect to systemic disease, the use of rituximab was supported by a large number of studies, mainly uncontrolled. We are also very far from defining specific treatment targets (especially searching for remission in non-systemic features), but it may be useful to use the EULAR disease activity states,[70] considering that any higher disease activity has to be regarded as inadequate disease control, thus mandating a therapeutic intervention, or that low disease activity achieved after therapy may be potentially acceptable for some organs. In any case, as stated in previous EULAR recommendations,[95] communication with the patient to clarify and agree on the treatment goal and the means to attain it is of utmost importance. Monitoring should be frequent in patients with systemic active disease, although the frequencies of follow-up examinations should be adjusted in accordance with the individual disease activity state,[70] namely, more frequently, such as monthly, when patients have high disease activity, and less frequently, such as every 6–12 months, when patients have low disease activity.

Lessons should be learnt from the first biological tested in primary SjS (infliximab). The excellent results of tumour necrosis factor-targeted therapies in RA led to their testing in patients with primary SjS, in spite of the large pathological and clinical differences between the two diseases. After the report of promising results in small open-label studies (one of which has been recently retracted by the authors), the first well-designed RCT showed no differences between the infliximab and placebo arms for the primary outcome. The same disappointing results have been obtained for other drugs reported as efficacious according to uncontrolled data (hydroxychloroquine and rituximab) without significant results for the primary outcomes when tested in RCTs. In SjS trials, two common issues may help to explain the negative results. The first is the choice of primary end-points. Most studies used composite primary outcomes based mainly on the subjective evaluation of dryness, fatigue, pain[96] ; the strong influence of personal and environmental factors on the intensity of this triad of symptoms could explain the lack of significant differences (a higher rate of placebo-related response), together with inadequate patient selection (too low degree of disease activity), the influence of concomitant drugs and the heterogeneity of diagnostic tests. The composite ESSDAI to measure systemic activity was used in the most recent RCT as a secondary end-point and frequently calculated retrospectively (although one of the weaknesses of this outcome could be the difficulty in differentiating activity due to chronic damage in different domains). The preliminary results of two new RCTs where ESSDAI was the primary end-point demonstrated efficacy of the active drug versus placebo (anti-CD40 and the combination of leflunomide and hydroxychloroquine).[97 98] The second issue is the limited number of patients randomised (no more than 50–60 patients per arm), taking into account the clinical and immunological heterogeneity of SjS as an SAD (such as SLE or systemic vasculitis); in SLE, the pivotal trials that allowed the licensing of belimumab were obtained from two trials including nearly 1000 patients each. Some promising results recently reported in small open-label studies testing biologics (belimumab, anakinra) must be confirmed in further large well-designed RCTs, while advance results of a large trial in primary SjS do not indicate a clinical benefit of abatacept.[99] The current therapeutic pipeline in SjS, as shown by the *clinicaltrials.gov* webpage, is that the biologic therapeutic approach overwhelmingly used in SjS until now (targeting B-cell depletion) is shifting towards the evaluation of biologics targeting cytokines, T-cells and intracellular signalling pathways.[100] With respect to ongoing trials, considerable interest is centred on the B cell survival factor (BAFF) pathway, investigating the effect of monoclonal antibodies targeting BAFF-receptor or the association between B-cell depletion and BAFF inhibition. In addition, studies are testing inhibition of other pathways activating B cells. Lastly, four ongoing trials are testing other pathways or the use of other cytokine-based therapies including tocilizumab, abatacept, filgotinib (a janus kinase inhibitor) and human recombinant Il-2.

Therapeutic research in SjS should probably be reconsidered in order to explore new pathogenic targets outside the glandular tissue (ie, neuroendocrine pathways), and to search for a more personalised therapeutic approach based on genetic, clinical, immunological and/or histopathological characteristics. It is not improbable that future RCTs would benefit from more selected patient cohorts, possibly including newly diagnosed SjS patients, the findings of early salivary gland ultrasound changes,[101–103] or evidence of early high disease activity at diagnosis[22] before permanent damage has been established and the changes are still reversible. Patients with sicca-limited disease differ from those with systemic disease, as do immune-negative patients from those carrying Ro autoantibodies or cryoglobulins, while recent etiopathogenic studies are beginning to divide SjS patients according to the genetic profile between those with or without a predominant IFN-I gene expression signature.[104–106] Sensitivity analyses searching for a differentiated response to therapies in these subsets of patients (sicca-limited vs systemic; Ro+ vs Ro-; positive vs negative salivary gland biopsy; positive vs negative IFN-I signature) might help to better delineate the therapeutic effect of a drug tested in primary SjS, although this would require a greater number of patients randomised than those included in reported trials.

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Box 1 Research agenda

- Is there a specific, differentiated treatment of lymphomas related to SjS?
- Is combination therapy a potential intervention to explore in SjS?
- Exploring targeted therapies against Th17 cytokines, IFNα, RORγt expression, Janus kinases (JAKS), STATs and mTOR intracellular pathways or interleukin-1.
- Searching for predictive factors of biological response.
- Potential use of sequential or intralesional use of biological therapies.
- Encouraging the development of new and innovative therapies.
- In what proportion of systemic patients is induction therapy with current therapeutic options effective in inducing sustained remission?
- Is the use of immunosuppressive and biologic agents safe and efficacious in the absence of concomitant glucocorticoid treatment?
- How safe and efficacious is the off-label use of other biologics after rituximab has failed?
- Can we find predictors of differential response to the synthetic and biological drugs used in SjS?
- Can we predict who will maintain remission after withdrawal of glucocorticoids?
- Will we be able to develop precision (personalised, stratified) medicine approaches in SjS? (IFN signature +/-; immunological or histopathological markers +/-)?
- Which biomarkers will help identify better predictors of poor outcomes?

In conclusion, the 2019 EULAR recommendations are based on the recent evidence collected on the management of primary SjS patients and on discussions by a large, broadly-based international TF. The recommendations synthesise current thinking on SjS treatment in a set of overarching principles and recommendations. These have been informed by a specific SLR on the efficacy and safety of topical and systemic interventions, although the high-quality scientific evidence focused on primary SjS patients fulfilling the currently-accepted sets of criteria was limited. However, the TF is convinced that adhering to these recommendations, including shared decision-making, assessing disease activity regularly with the ESSDAI instrument, and applying the sequence of drugs as proposed, will improve overall outcomes in a clear majority of patients with SjS. New research information on treatment strategies, predictive markers and other aspects will soon become available and will probably require an update of the recommendations in coming years (see Future Agenda box 1). Until then, we hope that the current recommendations will be broadly applied in clinical practice and/or serve as a template for national societies to develop local recommendations.

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