

Turkish Society for Rheumatology recommendations for topical and systemic treatments in Sjögren's disease

V. Yazısı¹, B. Armağan², N. İnanç³, C. Bes⁴, A. Doğru⁵, G. Sargın⁶, M.E. Yayla⁷, M. Ekici², G. Mumcu⁸, G. Karabulut⁹, E. Gönüllü¹⁰, H. Emmungil¹¹, N. Erdik¹², C.A. Yaşar¹³, D. Kerim¹⁴, E.A. Şener², A. Avcu³, E. Alpöz¹⁵, H. Çankaya¹⁵, M. Palamar¹⁶, S.A. Turhan¹⁷, Y. Kabasakal⁹

¹Department of Internal Medicine, Division of Rheumatology, Akdeniz University, Faculty of Medicine, Antalya;

²Clinic of Rheumatology, Ankara Bilkent City Hospital, Ankara; ³Department of Internal Medicine, Division of Rheumatology, Marmara University, Faculty of Medicine, Istanbul; ⁴Sağlık Bilimleri University, Başakşehir Çam And Sakura City Hospital, Istanbul; ⁵Department of Internal Medicine, Division of Rheumatology, Süleyman Demirel University, Faculty of Medicine, Isparta; ⁶Department of Internal Medicine, Division of Rheumatology, Aydın Adnan Menderes University, Faculty of Medicine, Aydın; ⁷Department of Internal Medicine, Division of Rheumatology, Ankara University, Faculty of Medicine, Ankara;

⁸Department of Oral and Maxillofacial Radiology, Faculty of Dentistry, Istanbul Okan University, Istanbul;

⁹Department of Internal Medicine, Division of Rheumatology, Ege University, Faculty of Medicine, İzmir;

¹⁰Department of Internal Medicine, Division of Rheumatology, Sakarya University, Faculty of Medicine, Sakarya; ¹¹Department of Internal Medicine, Division of Rheumatology, Trakya University, Faculty of Medicine, Edirne; ¹²Sakarya Training and Research Hospital, Sakarya; ¹³Kocaeli City Hospital, Kocaeli; ¹⁴Department of Internal Medicine, Division of Rheumatology, Ege University, Faculty of Medicine, İzmir; ¹⁵Department of Oral and Maxillofacial Radiology, Ege University Faculty of Dentistry, İzmir; ¹⁶Department of Ophthalmology, Ege University, Faculty of Medicine, İzmir; ¹⁷Department of Ophthalmology, Acibadem Mehmet Ali Aydınlar University, School of Medicine, Istanbul, Turkey.

Abstract

Objective

The aim of this work was to develop standardised recommendations for the treatment of Sjögren's disease (SjD) based on existing evidence and expert opinion.

Methods

The task force (TF) consisted of Turkish specialists in rheumatology, ophthalmology and dentistry with an interest in SjD. The group used the Population, Intervention, Comparison and Outcome (PICO) format to frame its clinical questions. A systematic literature review on the therapeutic management of SjD was subsequently conducted in accordance with PRISMA guidelines. Levels of evidence (LoE) were assigned according to the 2011 Oxford Centre for Evidence-Based Medicine (CEBM) standards.

Results

The recommendations are categorised under the following headings: general recommendations, management of ocular and oral dryness, and management of systemic organ involvements. Management of sicca symptoms benefits from a wealth of high-level evidence, highlighting topical therapies as the gold standard. Conversely, the treatment of systemic involvement relies heavily on case series and clinical experience. Here, glucocorticoids, hydroxychloroquine, and immunosuppressive agents remain cornerstone therapies. Overall, biologic therapies have demonstrated limited efficacy in SjD; however, they may be beneficial in selected patient subgroups and can be considered in cases of refractory systemic involvement.

Conclusion

The recommendations on SjD treatment, derived from a systematic literature review and clinical experience, will guide clinicians in the management of patients, based on a set of overarching principles.

Key words

Sjögren's disease, guidelines, evidence, treatment

Veli Yazısız, MD, Prof
 Berkan Armağan, MD, Assoc. Prof
 Nevsun İnanc, MD, Prof
 Cemal Bes, MD, Prof
 Atalay Doğru, MD, Prof
 Gökhan Sargın, MD, Prof
 Müçteba Enes Yayla, MD, Assis. Prof
 Mustafa Ekici, MD
 Gonca Mumcu, DDS, Prof
 Gonca Karabulut, MD, Prof
 Emel Gönüllü, MD, Prof
 Hakan Emmungil, MD, Prof
 Nilay Erdik, MD
 Canan Albayrak Yaşar, MD
 Duygu Kerim, MD
 Elif Akyazı Şener, MD
 Ayşegül Avcu, MD
 Esin Alpöz, DDS, Prof
 Hülya Çankaya, DDS, Prof
 Melis Palamar, MD, Prof
 Semra Akkaya Turhan, MD, Prof
 Yasemin Kabasakal, MD, Prof

Please address correspondence to:
 Veli Yazısız

Division of Rheumatology,
 Department of Internal Medicine,
 Prof. Akdeniz University,
 Faculty of Medicine,
 07070 Antalya, Turkey.
 E-mail: drvyazisiz@yahoo.com.tr

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Introduction

Sjögren's disease (SjD) is a systemically heterogeneous autoimmune disorder that primarily affects the exocrine glands but may involve multiple organ systems (1). Autoimmunity plays a crucial role in the pathogenesis of SjD, with various cells and cytokines involved in driving the inflammatory mechanisms. The management involves immunosuppressive agents to suppress inflammation, parasympathomimetics for symptomatic relief, and tear and saliva substitutes (2). Currently, numerous novel molecules, including antifibrotic agents, are under investigation and are considered potential future therapeutic options (3, 4).

The management of SjD requires a multidisciplinary approach, mainly involving rheumatologists, ophthalmologists, and dentists. Clinical guidelines serve as essential frameworks to guide clinicians in the management of patients. The first comprehensive guideline for the management of SjD was published by the British Society for Rheumatology (BSR) in 2017 (5). In late 2019, the European League Against Rheumatism (EULAR) published another set of recommendations regarding topical and systemic treatments in SjD management (6). A more recent guideline, updated by the BSR, covers not only treatment approaches but also diagnostic methods (7). Recommendations generally fall into two categories: symptomatic management of dryness and systemic immunosuppressive treatment. Additionally, organ-specific recommendations for the management of distinct systemic manifestations have been published (8, 9).

The need for updating existing guidelines and creating new recommendations arises from factors such as the introduction of novel agents for SjD treatment, new data on the efficacy of current drugs and increased experience from clinical practice. The aim of this initiative is to prepare a SjD treatment recommendation set to determine a common approach for SjD management, considering evidence based on medical literature and the experiences of rheumatology specialists and relevant stakeholders. For this purpose, a

systematic literature review was conducted, and a new guideline was prepared for the treatment of all organ involvements of SjD based on levels of evidence and clinical experience.

Methods

No support was received from the pharmaceutical industry at any stage of the project. Three co-coordinators (YK, VY and BA) were appointed by the Turkish Society of Rheumatology (TRD) to manage the coordination.

A task force

The task force (TF) comprised 22 members: 17 rheumatology specialists (including 5 clinical fellows/research assistants), 2 ophthalmologists, and 3 dentists. All participants declared potential conflicts of interest. This study is based on a systematic literature review and expert opinion; it does not include patient or public involvement.

Study design

The literature search was conducted in the PubMed, Web of Science, EMBASE, and Cochrane Central Library databases, encompassing studies published between 2017 and 2024. The present study exclusively encompasses English-language publications, with a particular emphasis on meta-analyses, systematic reviews, and clinical studies. The search strategy was guided by predefined keywords and headings related to therapeutic approaches in SjD. The review was conducted in accordance with the PRISMA 2020 guidelines and organised around predefined Population, Intervention, Comparison and Outcome (PICO) questions that had been approved by the TF. The adoption of this structured approach was driven by the objective of enhancing methodological clarity and supporting a more reliable interpretation of the available evidence. From the 1,383 records identified, 1,223 were excluded during the screening process, and 160 studies met the inclusion criteria (Fig. 1)

The SLR strategy was driven by 26 pre-specified PICO questions approved by the TF members (Supplement file). SLR was done for tissue/organ involvement and pregnancy outcomes for SjD

Competing interests: none declared.

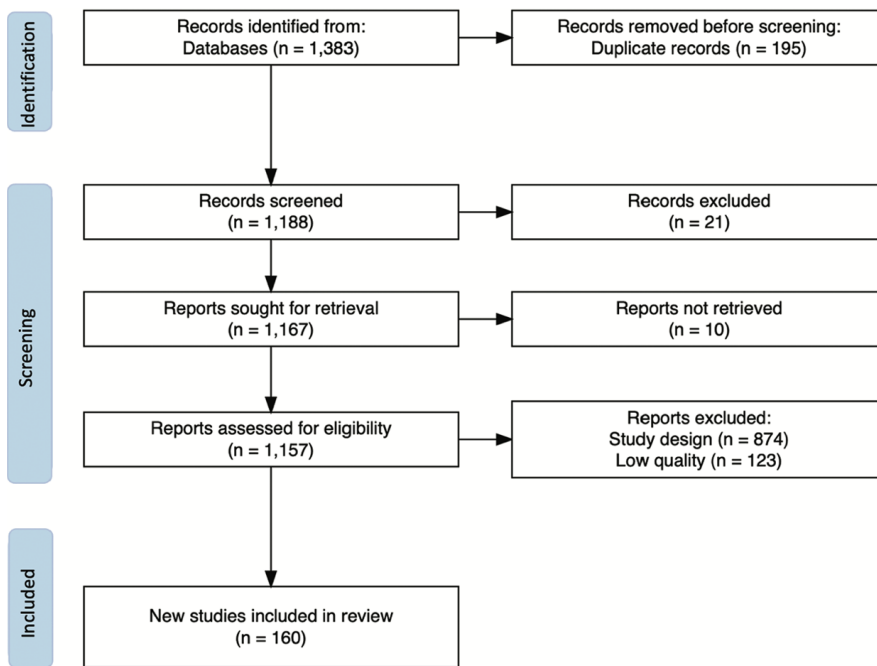


Fig. 1. PRISMA diagram.

based on these 12 headings: Oral, Ocular, Skin, Constitutional, Musculoskeletal, Neurological, Gastrointestinal, Haematological, Cardiac, Pulmonary, Urinary systems and Pregnancy-related approaches. The search was limited to adult populations. The term (Sjögren OR Sjögren OR "Sicca syndrome") was searched using 12 titles and keywords containing relevant treatment methods for each PICO. Reference lists of meta-analyses, systematic reviews, clinical trials, and randomized controlled trials were examined to identify additional studies. After full-text review, appropriate studies were selected for data extraction. Differences of opinion were resolved through discussion and consensus. The Oxford CEBM standards were used to grade the levels of evidence (LoE) and determine the strength of recommendation (10).

Evaluation of recommendations

The strength of each proposal was determined by considering the LoE, graded according to the 2011 Oxford Centre for Evidence-Based Medicine (CEBM) criteria, and the Level of Agreement (LoA), reached through structured voting among TF members. Proposals were approved when at least 80% of participants reached consensus.

This approach and its underlying reasoning are explained more clearly in the Methods section to enhance transparency and reproducibility. The results of the SLR were presented to the TF members, and draft recommendations were developed. Through further evaluations, the recommendations were finalised and voted on. The LoA for each proposal was voted on among the TF members; a minimum of 80% consensus was required. The questionnaire was distributed electronically to all members of the Turkish Rheumatology Association for an external vote. A total of 119 rheumatologists participated, assigning scores from 0 (completely disagree) to 10 (completely agree).

Results

SjD management requires the collaboration of different specialties due to multi-organ involvement. However, it is essential that rheumatologists remain primarily responsible for the overall management of SjD patients. It has been concluded that consultation with relevant specialties is necessary depending on the organ involvement, and thus a multidisciplinary approach should be adopted. Although evidence-based data are limited, this was adopted as a general recommendation with high

consensus. The recommendations are presented in Table I and II. (The Turkish version of our recommendations is presented in Supplementary Table S3 and S4).

Treatment of oral dryness

Maintaining oral health is fundamental to SjD management, requiring close collaboration between the rheumatologist and dentist. Patients should be educated on the significance of oral health, supported in maintaining effective oral hygiene practices, and regularly advised attending dental checkups for preventive care and early interventions. Expert opinion emphasises this tripartite partnership (rheumatologist, dentist, patient) for appropriate preventive strategies, minimising complication and early lesion diagnosis (11-13). Topical fluoride applications, use of fluoride-containing toothpastes, oral care with alcohol-free mouthwash, reducing alcohol, tobacco, spicy food, and sugary intake, and maintaining oral moisture by adequate water intake are all measures that can be taken to protect oral and dental health (14-22). Patients should be informed and encouraged to implement these preventative measures.

Protective measures for improving oral health include topical fluoride applications, regular tooth brushing, the use of fluoride-containing toothpastes, oral care with alcohol-free mouthwash, and lifestyle modifications such as reducing the consumption of alcohol, tobacco, spicy foods, and sugary products. Additionally, maintaining oral moisture through adequate water intake is essential. Patients should be informed and encouraged to implement these preventative measures in the disease management.

The severity of salivary gland involvement in SjD is determined by salivary flow rate (SFR) (6, 7). In patients with unstimulated salivary flow below 0.1 ml/min, the severity is further classified as mild, moderate, and severe, depending on the amount of stimulated SFR (Supplementary Table S2). Symptomatic management of dry mouth should be individualised based on the severity of glandular dysfunction, en-

Table I. Recommendations for the management of dryness symptoms and glandular involvement in Sjögren's disease.

	LoE	Vote (%)	LoA
General recommendations			
In Sjögren's disease, patient management should be carried out in a multidisciplinary manner, with the coordination of rheumatology specialists and the participation of relevant branches.	NA	99.8	9.57
Treatment recommendations for oral dryness			
It is recommended that patients be informed about the adverse effects of the disease on oral health, be motivated to maintain oral hygiene, and advised visiting a dentist every 3-6 months, depending on the severity of dryness.	4	95.9	9.00
Topical fluoride application, fluoride toothpaste, and alcohol-free mouthwash are recommended in dry mouth.	4	95.9	8.74
Patients with dry mouth are advised to limit their intake of alcohol, tobacco, spicy foods, carbohydrates and sugary products. They should also be informed about importance adequate water consumption and encouraged to moisten the oral cavity frequently with water.	4	97.7	9.64
Symptomatic treatment management for dry mouth can be planned according to the severity of dryness.	4	95.9	9.15
In mild glandular dysfunction, non-pharmacological stimulants such as sugar-free gum (containing aspartame, xylitol, or sorbitol) and lozenges can be used.	4	97.7	9.03
In moderate glandular dysfunction, pharmacological preparations can be used.	4	93.6	8.68
In severe glandular dysfunction, artificial saliva preparations, oral rinses, oral gels, and sprays can be used.	4	96.3	9.21
In cases where the pharmacological response for dry mouth is suboptimal, liquid or gel-form artificial saliva preparations may be used	4	95.4	8.82
Pilocarpine may be used in patients experiencing dry mouth who still retain residual gland function (stimulated salivary flow rate ≥ 0.1 mL/min), excluding those with contraindications such as glaucoma, heart disease, liver disease, respiratory conditions (like asthma), allergies, pregnancy, and lactation	1b	95.4	9.03
Glucocorticoids may be used short-term during acute parotid inflammation associated with SjD	5	95.4	8.92
Hydroxychloroquine sulfate use may be recommended in early-stage (<5 years) patients	2b	91.3	8.85
Azathioprine, methotrexate, mycophenolate mofetil and leflunomide are not recommended as primary treatment options in isolated salivary gland involvement.	2b	94.0	8.26
Rituximab and abatacept should not be prescribed solely for the management of dry mouth in the initial phase of treatment*. However, they may be used in patients in the early stage of the disease (<5 years) who have residual secretory potential (stimulated salivary flow rate ≥ 0.1 mL/min)*. These agents can be considered among treatment options for patients with concomitant rheumatoid arthritis.	*1b &1a	92.7	8.20
Treatment recommendations for ocular dryness			
The use of artificial tear preparations and ocular gels is recommended as the first step in dry eye treatment.	1a	95.7	9.75
Artificial tear preparations containing active ingredients like methylcellulose or hyaluronic acid should be used at least four times a day. If necessary, the frequency can be increased to as often as once per hour. Preservative-free artificial tears are recommended for patients requiring four or more applications daily.	1a	94.2	9.18
Ocular gels should be used before bed to control symptoms. Eyelid hygiene should be performed in the morning after using ocular gels to prevent blepharitis.	1a	94.7	9.36
Management of patients with persistent and/or severe dry eyes should be done in collaboration with ophthalmologists.	5	96.8	9.89
For those with resistant and/or severe dry eyes, the use of topical cyclosporine A-containing eye drops is recommended.	1b	93.1	9.15
Topical corticosteroid eye drops can be used as a bridge treatment for a short time (maximum 2-4 weeks) until the effectiveness of cyclosporine A becomes evident.	1a	93.1	8.51
Autologous or allogeneic serum eye drops may be used in patients who do not respond to or cannot tolerate topical cyclosporine A-containing eye drops.	1a	94.7	8.73
Oral muscarinic agonists (Pilocarpine and Cevimeline) and punctal plugs may be used as rescue therapy in patients unresponsive or intolerant to all treatments.	1c	91.5	9.10
Pilocarpine is recommended to improve glandular function, starting at 5 mg once daily and increasing to 4 times daily if needed.	1b	92.6	9.27
Systemic glucocorticoids, conventional immunosuppressives, or biologic agents are not recommended for the treatment of dry eye.	2c	94.2	8.84
In the treatment of meibomian gland dysfunction, it is recommended to apply a warm compress to the eyelid for at least 10 minutes a day.	1a	94.7	8.82
Oral or topical antibiotics with anti-inflammatory effects, such as doxycycline or azithromycin may be given in dry eyes with blepharitis.	2b	92.6	8.61
Lipid-containing eye drops or liposomal eye sprays may be used as adjunctive treatment in patients with dry eyes associated with meibomian gland dysfunction or blepharitis.	2c	92.6	8.54
SjD: Sjögren's disease; LoA: levels of agreement; LoE: levels of evidence; NA: not applicable.			

Table II. Recommendations for the management of systemic organ involvements in Sjögren's disease.

	LoE	Vote (%)	LoA
Treatment of constitutional symptoms			
Additional diseases that may cause fatigue (<i>e.g.</i> , anemia, hypothyroidism, fibromyalgia, etc.) should be excluded.	5	97.3	9.88
Walking and resistance exercises are recommended as non-pharmacological approaches to symptomatic treatment of fatigue.	2b	93.6	9.48
Hydroxychloroquine sulfate can be used in conjunction with non-pharmacological approaches*, biological agents are not only recommended for fatigue [®] .	*4 & 1b	93.6	9.55
Treatment of musculoskeletal involvements			
Non-steroidal anti-inflammatory drugs and/or hydroxychloroquine sulfate may be used in patients with arthralgia and/or myalgia; in cases with arthritis, additional low-dose glucocorticoids (≤ 7.5 mg/day prednisolone and equivalent), methotrexate, or low-dose cyclosporine may be used*. Rituximab and abatacept may be used in the treatment of arthritis unresponsive to all these treatments [®] .	*4 & 2b	94.7	8.99
Patients with SjD who develop myositis should be treated as if they had inflammatory myositis.	5	94.7	9.32
Treatment of pulmonary involvements			
Inhaled treatments are recommended as the first choice in patients with bronchial involvement.	4	91.5	8.72
In interstitial lung diseases, glucocorticoids and/or immunosuppressive treatments are administered, depending on disease severity. Mycophenolate mofetil is the first-line choice, whereas azathioprine, rituximab, and cyclophosphamide may serve as alternative options.	4	95.7	9.31
Antifibrotic treatments should be considered in patients who meet the definition of progressive pulmonary fibrosis.	4	91.0	8.64
Lung transplantation should be considered, through a multidisciplinary team assessment, for selected patients with persistent respiratory failure who are unresponsive to or fail maximal medical therapy.	5	92.6	9.10
Treatment of Neurological Involvements			
Treatment for central nervous system involvement involves glucocorticoids combined with a systemic immunosuppressant (<i>e.g.</i> , azathioprine, mycophenolate mofetil, methotrexate, or cyclophosphamide) or rituximab, depending on the severity. In cases of severe or refractory neurological involvement, IVIg and/or plasma exchange can be added to the regimen.	4	94.2	9.53
Treatment for motor and sensory peripheral neuropathies may use glucocorticoids combined with systemic immunosuppressive agents (azathioprine, mycophenolate mofetil, methotrexate, or cyclophosphamide), IVIg, plasma exchange and/or rituximab.	4	92.1	9.46
Rituximab is recommended as the treatment of choice for peripheral neuropathies associated with cryoglobulinemic vasculitis.	1b	96.8	9.56
Gabapentin or pregabalin should be considered for the symptomatic treatment of isolated sensory neuropathies and small fiber neuropathies.	4	94.2	9.25
Treatment of skin involvements			
In cases of non-vasculitic skin involvement, including annular erythema and subacute cutaneous lupus lesions, topical treatments (topical steroids and/or tacrolimus) and/or systemic therapies (hydroxychloroquine sulfate and/or glucocorticoids) may be applied. Alternatives are methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, or colchicine if there is inadequate response or glucocorticoid dose cannot be reduced.	4	93.6	9.38
Systemic glucocorticoids are recommended for vasculitic skin involvement*. If there is no response or the dose cannot be reduced, colchicine, methotrexate, azathioprine, mycophenolate mofetil*, or rituximab may be used. Rituximab is the primary treatment option in patients with cryoglobulinemia [®] .	*4 & 1b	92.6	9.56
Treatment of haematological abnormalities			
Systemic glucocorticoids may be used in autoimmune hemolytic anaemia*. If there is insufficient response or the dose cannot be reduced, rituximab* or azathioprine [®] may be used.	*4 & 5	93.1	9.56
For immune thrombocytopenia, systemic glucocorticoids may be used. In cases of non-response or when the dose cannot be reduced, azathioprine, mycophenolate mofetil, cyclophosphamide, rituximab, or calcineurin inhibitors can be available. IVIg should be utilised for resistant or symptomatic presentations.	4	93.1	9.53
Treatment is not recommended for asymptomatic lymphopenia.	5	93.6	9.03
Hydroxychloroquine sulfate therapy may be used in the presence of hypocomplementemia and/or hypergammaglobulinemia.	4	92.6	8.69
Treatment of gastrointestinal symptoms			
Symptomatic treatments (Proton pump inhibitors, antacids, H2-receptor blockers and prokinetics) can be used to palliate gastrointestinal symptoms.	5	92.1	9.42
Treatment to cardiac involvements			
Glucocorticoids, hydroxychloroquine sulfate and/or immunosuppressives (azathioprine, belimumab, rituximab, cyclophosphamide) may be given to patients with cardiac involvement.	4	91.0	9.18
Colchicine should be used in patients with pericarditis and/or pericardial effusion.	4	92.1	8.37
The management of arrhythmias should be made shared decision-making with cardiology specialists.	5	93.1	9.81

	LoE	Vote (%)	LoA
Treatment to renal and urinary system involvements			
Symptomatic treatment and/or glucocorticoids may be used depending on the severity of the disease in tubulointerstitial nephritis and/or distal renal tubular acidosis. Immunosuppressives (azathioprine, cyclosporine, mycophenolate mofetil, rituximab) can be used if unresponsive to treatment or in the presence of moderate/high disease activity.	4	94.7	9.23
Glucocorticoids should be the first-line treatment for glomerulonephritis. Immunosuppressives (azathioprine, mycophenolate mofetil, calcineurin inhibitors, cyclophosphamide, and rituximab) may be used depending on disease severity and the type of glomerulonephritis.	4	95.2	9.44
In cryoglobulinemic vasculitis, high-dose glucocorticoids can preferably be combined with rituximab*, alternatives are azathioprine, mycophenolate mofetil, or cyclophosphamide. In resistant or rapidly progressing cases, plasma exchange may be added as an adjunctive treatment*.	*1b *4	95.7	9.60
Glucocorticoids can be administered as monotherapy or combined with immunosuppressive agents (azathioprine, calcineurin inhibitors, or mycophenolate mofetil) for interstitial cystitis.	4	91.0	9.01
Approaches to pregnancy			
It is recommended to ensure disease control before pregnancy, and to perform a risk assessment.	5	96.8	9.85
The use of hydroxychloroquine sulfate is recommended to prevent the development of cutaneous neonatal lupus in pregnant women with anti-Ro (+) and/or anti-La (+).	3	95.2	9.20
In pregnant women with Anti-Ro (+) and/or Anti-La (+), evaluation with fetal echocardiography is recommended starting from the 16th week of pregnancy for the development of congenital heart blocks.	5	97.3	9.88
Hydroxychloroquine sulfate ^{&} is recommended for the primary* and secondary prevention of congenital heart blocks in pregnant women who are anti-Ro (+). Treatment with betamethasone or dexamethasone, intravenous immunoglobulin (IVIg), or plasma exchange is advised for pregnancies in which incomplete or complete fetal heart blocks have developed ^z .	*5 *2b ^z 4	95.2	9.48

sure that therapeutic interventions align with the patient's residual salivary function and clinical presentation (23-25). In cases of mild glandular involvement, non-pharmacological interventions that stimulate salivary gland function may be sufficient. Evidence supports the use of sugar-free chewing gum containing aspartame, xylitol, or sorbitol, and lozenges to promote salivary stimulation (14, 26-28). The use of artificial saliva preparations, oral rinses, sprays and gels should be used to reduce the symptoms of advanced dryness in patients without residual glandular tissue (15, 16, 27, 29-35). Current evidence is insufficient to support the effectiveness of alternative approaches such as acupuncture, electrostimulation, and gargling with coconut or olive oil in the management of dry mouth symptoms (36, 37).

Systemic treatment effects on major salivary glands were evaluated by assessing improvements in four key variables: functional status (stimulated/unstimulated flow rates), subjective dry mouth symptoms (Visual analog scale (VAS) 0-100 mm), structural imaging changes, and histopathological changes. The presence of residual glandular tissue is determined based on stimulated/unstimulated SFR values (6). While

assessing SFR, the early stage of SjD is defined as a disease duration of ≤ 5 years, whereas the long-standing stage is characterised by a duration of ≥ 10 years (38).

In two placebo-controlled studies on pharmacological stimulation of the salivary glands with pilocarpine hydrochloride positive effects such as increased SFR, decreased dry mouth symptoms, decreased dry saliva and decreased water requirement were observed within 12 weeks of treatment (39, 40). Non-pharmacological approaches should be preferred for the symptomatic management of mild dryness. Artificial saliva substitutes are recommended for patients with severe glandular dysfunction, where residual secretory tissue is absent. In cases of moderate dryness with preserved glandular function, pharmacological stimulation may be considered alongside non-pharmacological interventions to enhance salivary output and symptom relief. The recommended dose for pilocarpine hydrochloride is 20 mg/day.

In an open prospective study, low-dose prednisolone (mean starting dose 15 mg, maintenance dose 5-7.5 mg) resulted in an increase in SFR and a decrease in subjective symptoms (41). Furthermore, it is known that glucocorticoids

are used to suppress parotid attacks due to their anti-inflammatory activity.

The results of studies evaluating the effect of hydroxychloroquine sulfate (HCQ) are conflicting; however, a meta-analysis reported a moderate improvement in oral symptoms and unstimulated SFR (42). In a double-blind, placebo-controlled study of patients with a median disease duration of 3 years and who had not used HCQ, corticosteroids or immunosuppressants in the last 3 months, no significant difference was found with 400 mg daily treatment (43). An open-label study (n=14) reported reduced parotid swelling and partial improvement in dry mouth with HCQ 200 mg daily for 12 months, though objective SFR remained unchanged (44). Conversely, a retrospective study (n=40) demonstrated an increase in SFR (Saxon test) after 6 months (45). However, a large randomized controlled trial (RCT) (n=120) evaluating HCQ showed a 30% reduction in subjective oral dryness but no increase in SFR was observed (46). Reanalysis of the RCT further complicated findings: SFR improved in the "low disease burden" group at week 24, while the "high disease burden" group showed improvement in the EULAR Sjögren's Syndrome Patient Re-

ported Index (ESSPRI) dryness score (47). There is also other evidence, both prospective and retrospective, that HCQ increases SFR (48, 49).

Oral manifestations of SjD have not shown consistent or significant improvement across studies using various immunosuppressive agents like azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), and leflunomide (LEF), with some studies noting only subjective or minor changes without improvement in objective measures such as SFR (50-53).

Rituximab (RTX) is the most extensively studied biologic agent in patients with SjD. Its impact on SFR and dryness symptoms remains inconsistent and controversial across multiple studies. While early or selected-patient studies showed some promise for RTX in improving SFR, large, high-quality RCTs have generally failed to demonstrate significant efficacy for dry mouth symptoms or objective salivary function compared to placebo (54-60). Meta-analyses also yield heterogeneous results: one meta-analysis suggested that SFR was more likely with RTX when disease duration was ≤ 3 years (61); another, with a low level of evidence, reported no difference in dry mouth measured by visual analog scale (VAS) (62). Studies have reported conflicting findings regarding ultrasonographic changes in the salivary glands following RTX treatment, and these changes have not been consistently associated with improvements in SFR (63, 64). In the TEARS study, it was reported that patients with high ultrasound or histopathologic focus scores were reported to show no clinical response to RTX (65). Several studies have evaluated the efficacy of the biologic agent abatacept. While open-label, prospective observational studies reported an increase in SFR (66-68), others have demonstrated the opposite, showing it to be ineffective (69), and RCTs have not shown significant efficacy (70, 71).

Treatment of ocular dryness

Dry eye is observed in more than 95% of patients and constitutes a major determinant of quality of life. Ocular sur-

face staining and the Ocular Surface Disease Index (OSDI) score are used to assess the severity of dry eye (72-73). An OSDI score ≥ 33 indicates *severe dry eye*, and patients who fail to improve despite using the maximal-dose and duration of artificial tears and gels used in standard care are considered to have *refractory dry eye* (Supplementary Table S2). In patients with severe or refractory dry eye, artificial tear therapy may be inadequate, and other pharmacological treatment options or surgical interventions may be considered. Multidisciplinary collaboration between rheumatologists and ophthalmologists is crucial in determining the treatment approach.

The first-line approach for the symptomatic management of dry eye involves artificial tear preparations and ocular gels. Results from RCTs and meta-analyses indicate that most artificial tear preparations share similar efficacy, proving to be an effective and safe treatment option (74). Commonly used preparations contain methylcellulose or hyaluronic acid. These agents, which have no systemic toxic effects, can be administered at various levels and doses, including hourly instillations, depending on the severity of dryness. Ocular gels are particularly recommended for use before bedtime, and treatment should be complemented with eyelid hygiene in the mornings (75).

Topical cyclosporine A is an effective treatment for dry eye, primarily by improving lacrimal gland function and reducing ocular surface inflammation (76). Its use is recommended for patients with severe dryness refractory to artificial tears and ocular gels. Cyclosporine A has also demonstrated efficacy in an eight-week RCT (77). Separately, although the efficacy of 0.03% tacrolimus eye drops was shown in one prospective double-blind study (78), its clinical use is limited by a lack of broader supporting evidence. Furthermore, topical glucocorticoid preparations serve as another option for patients with refractory and severe dry eye; however, their duration of use must be minimized due to the potential for ocular toxicity and an increased risk

of infection (75, 79).

Autologous serum eye drops, a treatment with superior lubricating properties due to their similarity to natural tears, are effective for short-term symptom relief in refractory dry eye, but their widespread clinical use is limited by contamination risks and the need for cold chain storage. A meta-analysis has demonstrated their potential for short-term improvement in dry eye symptoms (80). They are recommended by many experts for cases refractory to other topical treatments, with clinical experience likewise reporting favourable outcomes (75, 81-83).

Punctal occlusion is a therapeutic procedure for dry eye that mechanically blocks tear drainage to keep natural tears on the eye surface longer. However, a meta-analysis of 18 studies involving 711 patients found heterogeneous results, making its benefit for improving symptoms uncertain (84). While generally safe, potential complications include epiphora and dacryocystitis.

Pilocarpine hydrochloride acts as a secretagogue, stimulating saliva production through muscarinic receptors. Its effectiveness for both dry mouth and dry eyes has been evaluated in single- and multicenter RCTs. Doses range from 10 mg to 30 mg are reported to be well-tolerated, to lessen dry eye symptoms, and to enhance rose bengal staining scores (39, 40, 85). Likewise, cevimeline hydrochloride, a specific M3 muscarinic receptor agonist, has proven effective and safe for treating dry eye symptoms linked to SjD when administered at 20-30 mg three times daily (86, 87).

Hydroxychloroquine (46, 88), AZA (20, 50), MTX (51), LEF (51, 89, 90) and MMF (52, 91) have been evaluated in controlled trials, but their efficacy for dry eye has not been demonstrated. Although, RTX has been shown to improve lacrimal gland function, it did not alleviate dry mouth (62). Furthermore, belimumab was found to have no effect on either salivary flow or the Schirmer's test (92). Consequently, based on the current evidence, the TF does not recommend the use of systemic immunosuppressive agents for

the treatment of dry eye.

Various therapeutic approaches are available for relieving dry eye symptoms secondary to meibomian gland dysfunction, including lid warming, thermal pulsation, antibiotics, lipid-containing eye drops, and perfluorohexyloctane. In cases complicated by infections like blepharitis, the use of systemic or topical antibiotics is supported by sufficient evidence. Furthermore, systematic reviews of controlled clinical trials suggest a benefit from treatments such as lid warming, antibiotics, lipid-containing eye drops, or liposomal eye sprays (93-95).

Treatment of constitutional symptoms

Symptoms such as weakness and fatigue are common in SjD. These symptoms are accompanied by other findings, such as psychological problems and insomnia, resulting in a deterioration in the patient's quality of life. Mechanisms involved in the pathogenesis of the disease may play a role in the fatigue in SjD. However, SjD itself may not be the sole cause of fatigue. Many systemic diseases can contribute to the development and severity of fatigue (96, 97). Therefore, it is necessary to investigate and treat other coexisting psychological and organic disorders. Several studies have investigated the effectiveness of non-pharmacological approaches in reducing fatigue. A study showed that supervised walking, three times per week, was a safe and feasible approach that improved fatigue level (FACIT-Fatigue) and depressive symptoms (98). A review found that intense aerobic exercise reduced fatigue and depressive symptoms but had no effect on anxiety, as assessed by the Health Assessment Questionnaire (HAQ) (99). Similarly, a study in 40 patients found that non-invasive vagal stimulation improved fatigue (fVAS) (100). A double-blind study also showed that transcranial direct current stimulation reduced fatigue and was a reliable method (101). The TF members accepted that walking and resistance exercise be recommended to patients because they are lifestyle changes that can be easily implemented by the patients; non-invasive vagal stimulation

and transcranial direct stimulation are approaches with potential for application if their effectiveness is supported by other studies.

The JOQUER study reported that HCQ had no significant effect on fatigue (46). However, subgroup analyses have shown that extended treatment up to 24 weeks may reduce fatigue in some patients (47). A meta-analysis of 215 patients, including four studies, found HCQ to be less effective than placebo in alleviating fatigue (102). Clinical experience with HCQ, a widely used agent in the treatment of connective tissue diseases, particularly SLE, is quite extensive. So, the TF decided that HCQ may be used for the palliative management of fatigue.

In SjD, the effects of many biological agents, especially RTX, on fatigue have been investigated (55, 57, 58, 71, 92, 103-112). Cost and accessibility of biological agents, as well as their efficacy results, are limitations to their use only for fatigue.

Treatment of musculoskeletal involvement

Arthralgia, arthritis and myalgia are common in SjD and must be treated to improve patients' quality of life and satisfaction. The most commonly used and effective agents for relieving joint complaints are systemic or topical nonsteroidal anti-inflammatory drugs (NSAIDs) (113).

Glucocorticoids, also used in the systemic organ involvement of SjD, are effective in suppressing many types of inflammatory arthritis, particularly rheumatoid arthritis. A similar situation applies to MTX. Although there is no definitive evidence for its efficacy in SjD, glucocorticoids and MTX are widely used agents in the treatment of arthritis and tenosynovitis. Retrospective analyses have shown HCQ to be effective in treating both arthritis and arthralgia (114). A RCT revealed HCQ more effective than placebo in reducing joint pain (46). In a pilot study, low-dose cyclosporine A was found to be effective in reducing the number of swollen and tender joints (115). A RCT evaluating the efficacy of RTX showed a reduction of the number of

tender joints (104). Open-label studies about abatacept also demonstrated the decrease of overall disease activity (69, 106). Off-label use of biologic agents via the approval of the health authority for the treatment of arthritis unresponsive to other treatments, particularly RTX, is common in clinical practice. In the presence of inflammatory myositis in patients with SjD, it is appropriate to accept the primary disease as inflammatory myositis, and SjD is the secondary form. Systemic treatments should be planned according to the severity of inflammatory myositis and organ involvement than SjD.

Treatment of pulmonary involvement

The frequency of pulmonary involvement in SjD is between 9-22% and includes manifestations from chronic cough to interstitial lung disease (ILD) (116). ILD involvement can be progressive and increase mortality (117, 118). In most cases of bronchial involvement, lung function remains preserved, and deterioration is very slow; association with respiratory failure and death is rare. Systemic immunosuppressive drugs are not reported as necessary for minor airway changes or bronchiolitis (119). Furthermore, isotonic saline nebulization can alleviate voice changes caused by chronic airway dryness (120, 121). Liposomal inhalation therapy has also shown positive effects on laryngeal symptoms and signs of dryness (122).

The combination of immunosuppressive agents and corticosteroids remains the most common treatment approach for connective tissue disease (CTD)-associated ILD. A retrospective case-control study on AZA demonstrated the presence of patients with improved or stable forced vital capacity (FVC) measurements (123). MMF has been shown to be well-tolerated in the treatment of CTD-associated ILD, including SjD, providing stability and improvement in pulmonary function and reducing the need for steroid dosage over a 2.5-year follow-up period (91, 124, 125). RTX has been effective in improving clinical symptoms and gas exchange and stabilizing the high-resolution computed tomography (HRCT)

score in SjD patients with ILD (126), and it has also been shown to be safe for use in other manifestations of SjD (60, 127). A retrospective review demonstrated that AZA, MMF, and RTX had similar effects on lung function, achieving stabilisation in pulmonary function tests, regardless of the involvement patterns in SjD-ILD (128). Furthermore, clinical observational studies involving a small number of SjD patients have reported that cyclophosphamide may also be effective in CTD-ILD (129, 130). However, the increased side effects of cyclophosphamide compared to other immunosuppressants limit its widespread use (131).

Recently, antifibrotic agents have shown promise in the treatment of ILD. Specifically, nintedanib and pirfenidone are agents approved for their demonstrated efficacy in treating idiopathic pulmonary fibrosis (IPF), with nintedanib also approved for use in systemic sclerosis related ILD (132). A RCT demonstrated that nintedanib reduces FVC loss in rapidly progressive fibrotic ILDs, with the effect being more pronounced in the UIP-like fibrotic pattern (133). A case series has also been published, demonstrating that nintedanib, when combined with immunosuppressive agents, provides improvement in FVC values, as well as stabilization and regression of HRCT findings in CTD-ILD (134). Despite low levels of evidence in SjD and based on data from other CTD-ILD patients, nintedanib can be added to the treatment regimen for SjD-ILD patients whose progression is observed despite the use of immunosuppressive agents. Clinical practice suggests that this need is particularly high in cases with a usual interstitial pneumonia (UIP) pattern.

Lung transplantation should be considered in patients with severe and progressive respiratory failure who fail medical treatments. The suitability of patients for heart and lung transplantation should be assessed by a pulmonologist and a thoracic surgeon (135).

Treatment of neurological involvements

The spectrum of neurological mani-

festations in SjD is broad, encompassing dysfunction of the central, peripheral, and autonomic nervous systems. At the core of this involvement are immune-mediated neuronal damage associated with autoimmunity, and a secondary mechanism where disease-related vasculitis causes ischemic or inflammatory neuronal injury. Central nervous system (CNS) involvement often mimics MS-like demyelinating diseases, the other manifestations are white matter lesions, optic neuritis, cognitive dysfunction, transverse myelitis, meningeal involvement, and ischemic cerebrovascular events related to vasculitis. Peripheral nervous system (PNS) involvement results in findings associated with motor and sensory neuronal damage, including small fiber neuropathy, sensorial and sensorimotor polyneuropathies, and mononeuritis multiplex. Autonomic dysfunction, however, presents with orthostatic hypotension, cardiac arrhythmias, and gastroparesis. Diagnosing autonomic neuropathies is more challenging, requiring screening with tests like heart rate variability, tilt-table testing, and quantitative sudomotor axon reflex testing.

Neurological involvements are among the life-threatening involvements, but treatment strategies are largely based on clinical experience. Glucocorticoids are the most commonly used agents, and while the starting dose is typically high, varying based on the severity and progression rate of the disease, dose reductions begin after 2-3 weeks, reaching lower maintenance doses within a few months. Immunosuppressives need to be added to glucocorticoids to alleviate neurological disorders and maintain relapse-free survival.

The immunosuppressive agents commonly used for CNS involvement in systemic autoimmune diseases are AZA, MMF, MTX, or cyclophosphamide (136, 137). There is also evidence supporting the use of biologic agents in CNS involvement. A prospective registry study that followed 78 patients using RTX demonstrated that, when combined with glucocorticoids and other immunosuppressives, RTX treatment led to improvement in systemic

involvement, including both CNS and PNS. It was also associated with a reduction in required steroid dosage (60). For CNS involvement in SjD, the level of evidence for plasma exchange (PLEX) and intravenous immunoglobulin (IVIg) therapies is low; however, case reports suggest they can be effective in selected patients (138). In cases of involvement refractory to other treatments, PLEX and IVIGs may be added to the therapeutic regimen. In some patients, anti-convulsant, anti-psychotic, and anti-depressant agents may be necessary, and their management should be evaluated by specialists in neurology and psychiatry.

Treatment approaches for PNS lesions are largely retrospective case studies. Evidence demonstrates the beneficial effects of corticosteroids, cyclophosphamide, and RTX, while AZA, MTX and MMF have also been successfully used for PNS involvements (139). IVIg has been reported to be effective and safe in the treatment of ataxic sensory neuronopathy (140). The combined use of RTX with glucocorticoids and other immunosuppressive agents has also been shown to improve PNS involvement. RTX has been reported to be a well-tolerated, effective, and to reduce serum B-cell biomarkers (69, 141). Although the SjD status of the included patients was unknown, a RCT demonstrated that an initial response was good to RTX in patients with cryoglobulinemic vasculitis-associated peripheral neuropathy, but the effect diminished at 24 months (142). Small fiber neuropathies, manifested by thermal sensory loss, allodynia, and/or hyperalgesia, are common but difficult to diagnose. Its diagnosis relies on clinical suspicion and requires complex testing, such as epidermal nerve fiber density on skin biopsy, laser-evoked potentials, heat and cold thresholds, and electrochemical skin conductance. Analgesics are largely ineffective in reducing the pain of small fiber neuropathy. Based on other neuropathic pain experiences, antidepressants, pregabalin, and gabapentin can be used for symptomatic treatment (143).

The autonomic nervous system is affected in SjD (144, 145). Vagal nerve

stimulation may have therapeutic potential for symptoms of autonomic neuropathy (146). However, there is no fully proven effective approach for the treatment of autonomic neuropathies.

Treatment of skin involvement

Skin lesions range from dryness to severe vasculitis. Annular erythema, papules, urticarial vasculitis, and palpable and nonpalpable purpura are among the more frequently observed lesions. Less commonly observed are vitiligo, alopecia, Sweet syndrome, lichen planus, granulomatous panniculitis, subcorneal pustular dermatosis, erythema elevatum diutinum, erythema multiforme and erythema nodosum-like lesions. In the presence of cutaneous vasculitis, lymphoma and cryoglobulinemia should be investigated (147).

Annular erythema can be treated with topical glucocorticoids and tacrolimus preparations. In persistent lesions unresponsive to topical treatments, low-dose glucocorticoids are effective, and clinical response is rapid (148, 149). HCQ may also be an option (150). Cases of successful treatment with low-dose cyclosporine have also been reported (151).

The treatment of vasculitic skin lesions should be determined by the extent of the vasculitis. While systemic glucocorticoids are generally used in clinical practice, systematic literature reviews also emphasize the effectiveness of glucocorticoids and immunosuppressive agents (152). For this purpose, analyses regarding the use of cyclophosphamide, AZA, and MTX have been published (153, 154). An open-label pilot study has also demonstrated the effectiveness of MTX in treating purpura (51). Furthermore, the effectiveness of colchicine treatment has been reported in hypergammaglobulinemic purpura and non-cryoglobulinemic vasculitis (155, 156). Finally, RCTs have shown RTX to be effective and safe in cryoglobulinemic vasculitis (56, 157).

Treatment of haematological abnormalities

Various benign or malignant hematological manifestations may be observed in SjD. Benign hematologic manifesta-

tions include autoimmune hemolytic anemia, immune neutropenia, lymphopenia, and thrombocytopenia, as well as serologic disorders like hypergammaglobulinemia and cryoglobulinemia. Although reactive lymphadenopathy is frequently observed, large or persistent lymphadenopathy should raise suspicion for lymphoma. The risk of lymphoma is increased in SjD and is associated with increased mortality (117, 158). Low serum complement levels are not uncommon laboratory findings in SjD and are independently associated with certain clinical, immunological features and mortality (159-161).

Glucocorticoids and immunosuppressive agents are used in the treatment of immune cytopenias that develop in SjD and other autoimmune diseases (162-165). HCQ is the most experienced agent (47, 102). Recent studies show that biologic agents are also effective in hematologic manifestations (69, 71, 92). Open-label studies have shown that sirolimus is effective in the treatment of immune thrombocytopenias (166, 167). There is also experience with cyclophosphamide in immune thrombocytopenias, but its use has decreased due to its toxic effects and the availability of newer agents such as MMF and RTX.

IVIg infusions are generally administered as salvage therapy for autoimmune thrombocytopenias refractory to other treatments (168). Its use is limited by factors such as its high cost and the necessity of obtaining health authority authorization for its off-label use.

Mild/moderate neutropenia and lymphopenia are common but are rarely associated with clinical problems. A neutrophil count below 500/mm³ increases the risk of serious bacterial infection, and a lymphocyte count below 1000/mm³ increases the risk of viral infection. In severe neutropenia, neutrophil counts can be increased with G-CSF. There is no proven agent for lymphopenia.

Persistent hypergammaglobulinemias are associated with glandular and severe diseases. It is thought that lowering IgG levels may reduce the progression of organ damage. HCQ and cor-

ticosteroids significantly reduce IgG levels (169). Therefore, HCQ may be considered in patients with hypergammaglobulinemia.

Treatment of gastrointestinal symptoms

Beyond dryness, gastrointestinal (GI) manifestations frequently observed include dysphagia, chronic atrophic gastritis, esophageal dysmotility, lymphocytic colitis, primary biliary cholangitis, and autoimmune hepatitis (170). The coexistence of chronic atrophic gastritis and autoimmune gastritis have further been documented (171). Dyspeptic complaints affect approximately one-quarter of patients, and associated gastritis may lead to decreased acid production and the presence of anti-parietal cell antibodies. Pernicious anemia may develop rarely (172). Other documented GI issues in SjD include irritable bowel syndrome and pancreatic exocrine insufficiency (173).

There is extensive clinical experience that gastrointestinal symptoms are common in SjD (174). However, there are no controlled studies or evidence for the use of immunosuppressive agents for GI involvements. Relief of GI symptoms is necessary and important for quality of life. Proton pump inhibitors, H₂ receptor blockers, antacids, and prokinetic agents known to be effective in relieving symptoms should be utilised.

Treatment to cardiac involvements

SjD significantly elevates the risk of atherosclerosis, driven by the synergistic effect of traditional risk factors and chronic inflammation and endothelial damage. Furthermore, SjD is associated with direct inflammatory cardiac manifestations, including pericardial effusion, pericarditis, and myocarditis. Arrhythmias, such as atrioventricular blocks, are also reported (175).

Currently, prospective studies specifically targeting the improvement of cardiac manifestations in SjD are lacking. Treatment evidence is primarily derived from clinical experience and case series, with immunosuppressive agents, particularly glucocorticoids, considered effective for treating these manifestations. Pericarditis and myo-

carditis are primarily managed with immunosuppressive agents. Pericarditis may also respond to NSAIDs and colchicine treatment. Arrhythmias may necessitate interventional approaches, such as pacemaker implantation. Standard therapies for heart failure are employed, which include diuretics, angiotensin-converting-enzyme inhibitors, β -blockers, and digoxin, often in addition to necessary immunosuppressive therapy (175-177).

The development of pulmonary hypertension in SjD, whether due to primary vascular remodeling (pulmonary arterial hypertension, PAH) or secondary to ILD, is a critical factor driving adverse outcomes and increased mortality in these patients (178). Specific therapeutic strategies are available for CTD-PAH, utilising monotherapy or combination regimens. These agents include calcium channel blockers, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogs, and prostacyclin receptor agonists. Currently, comparative studies for SjD-PAH therapies do not exist. Furthermore, in RCTs for overall CTD-PAH, the number of patients with SjD-PAH is typically very low or non-existent. Consequently, the current recommendation is to monitor patients with SjD for the development of PAH and to initiate treatment according to current PAH guidelines. These guidelines are largely based on evidence derived from systemic sclerosis-associated PAH (SSc-PAH).

Treatment to renal and urinary system involvement

Various manifestations of the kidneys and urinary system can be observed in SjD. However, these findings are often subtle and can be overlooked in clinical practice. This category primarily affects the renal tubules and is characterized by functional disturbances such as hypokalemia, acidosis, and nephrogenic diabetes insipidus. Glomerular pathology is frequently observed as membranoproliferative glomerulonephritis. This involvement may also represent part of the systemic vasculitic manifestations of SjD, particularly

those associated with cryoglobulinemia (179). There are no prospective RCTs addressing renal involvement in SjD. Evidence from case series and clinical experience guides treatment. The treatment approach for renal involvement in SjD varies based on the pathology: Hypokalemia and metabolic acidosis are managed symptomatically. Glucocorticoids are the primary treatment for severe cases of tubulointerstitial nephritis and glomerulonephritis. If the condition is severe or unresponsive to glucocorticoids, various immunosuppressive drugs are employed. These agents may include AZA, MMF, calcineurin inhibitors, cyclophosphamide, and RTX (153, 154, 179-189). Importantly, RCTs have specifically demonstrated the efficacy of RTX in treating glomerular pathologies associated with cryoglobulinemic vasculitis (142, 190). The combination of RTX plus corticosteroids demonstrated greater therapeutic efficacy, though it was also associated with severe infections, particularly when high-dose corticosteroids were utilized, with no difference in overall death rates (191). Therapeutic apheresis successfully treats severe renal involvement in cryoglobulinemic vasculitis (192). SjD patients with interstitial cystitis have been treated with corticosteroids; immunosuppressants have been used in refractory cases (193-195).

Approaches to pregnancy

Pregnancy in women with SjD carries distinct risks for both the mother and the fetus. The presence of anti-Ro/La antibodies puts the fetus at risk for congenital heart block and neonatal lupus. Antiphospholipid antibodies significantly increase the risk of miscarriage, preterm birth, and intrauterine fetal demise. These risks require pre-pregnancy evaluation, and disease activity must be suppressed using appropriate medications at least six months prior to conception (196).

Anti-Ro/La antibodies can cross the placenta starting at the 11th week of pregnancy and can lead to congenital heart block and neonatal lupus, which manifests as transient skin rashes, hepatic abnormalities, and cytopenias in newborns (197). During pregnancy,

rheumatologists and gynaecologists should collaboratively monitor both the mother and the fetus, and an examination of the newborn by neonatologists is immediately necessary. The gold standard diagnostic tool for congenital heart block is fetal echocardiography. Depending on operator experience, the correct diagnosis rate reaches 90%. Fetal echocardiography can visualise the cardiac anatomy, heart rate, rhythm and hydrops fetalis. In high-risk pregnancies, fetal echocardiographic monitoring should begin at 16 weeks, be repeated weekly until 24 weeks, and then bi-weekly until delivery (198).

In a multicentre open-label study, HCQ 400 mg/day reduced the incidence of second- and third-degree congenital heart block by nearly 50% (199). Another open-label case-control study showed that HCQ use reduced the risk of cutaneous neonatal lupus and delayed the onset of lesions (200). Therefore, the use of HCQ is recommended for secondary prophylaxis against congenital heart block as well as neonatal lupus in anti-Ro-positive mothers. In a prospective study, 12 anti-Ro/La-positive pregnant women whose fetuses developed congenital heart block were treated with weekly plasmapheresis, biweekly IVIg, and 4 mg daily betamethasone until delivery; neonatal IVIg administration immediately after delivery was also reported to be effective and safe in second-degree heart block (201). There are case series supporting these results (202).

Discussion

The development of this proposed guideline for managing glandular and systemic SjD manifestations involved the critical appraisal of both published evidence and clinical practice expertise. Composed of multidisciplinary experts working in Turkey, the recommendations primarily reflect the unique insights and challenges of the Turkish context.

In this context, it would be beneficial to evaluate the current recommendations alongside existing international guidelines. The EULAR recommendations and the recently updated British Rheumatology Society (BSR) guide-

lines offer evidence-based approaches to the management of SjD (6, 7). The current guideline aims to align with these international frameworks while offering a perspective informed by national clinical practice. The EULAR recommendations place significant emphasis on the distinction between topical and systemic treatments, with a substantial foundation in data derived from multinational cohorts and randomised controlled trials. Conversely, the BSR guidelines place greater emphasis on diagnostic pathways in addition to treatment strategies. The Turkish Rheumatology Society recommendations aim to complement these approaches by offering a more detailed, organ-specific treatment perspective that incorporates both current evidence and daily clinical experience in Turkey. In this context, the current guideline aims to support clinicians by adapting international evidence to local practice and providing practical guidance applicable to routine patient care. The drug doses recommended in this guideline are the doses obtained from clinical studies and case experience and are listed in Supplementary Table S5.

The major challenge encountered during the formulation of this guideline was the notable absence of standardised clinical outcome measures across the diverse manifestations of SjD. For example, fatigue was assessed using the VAS and HAQ in some trials, yet the Fatigue Severity Scale was used in others (99-101). In evaluating systemic involvement, some efficacy studies relied solely on organ-specific responses, while others utilised global disease activity indices such as the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI). The latter approach often made it difficult to precisely determine the impact of therapies on specific organ systems. Despite the variations in index choice, all responses were nonetheless interpreted against the predefined outcome methodology of the respective studies. This pronounced heterogeneity in trial endpoints significantly complicated the comprehensive assessment and synthe-

sis of the study results.

A frequent limitation in the literature is that most case-control studies involve low patient numbers, which subsequently diminishes the statistical robustness of the findings. Furthermore, the evidence base for the efficacy of agents in certain organ involvements extends beyond SjD-exclusive trials. The results of studies conducted on other autoimmune diseases, which share similar clinical and pathological features, have been necessarily considered and were partially influential. Furthermore, it is undeniable that the clinical experience of the TF members has been similarly developed in the management of manifestations lacking high-level evidence. Historically, comparative case-control studies on immunosuppressive drugs tended to focus on treating a single, specific organ involvement or merely reducing symptoms, rather than adopting a holistic approach to disease management. In contrast, more recent RCTs, primarily assessing the efficacy of biological agents, have evolved to employ disease activity measures that capture the full spectrum of disease manifestations.

This guideline is structured around the principles of applying currently available therapeutic agents, with a clear delineation of their supporting level of evidence. We explicitly do not provide recommendations for agents such as ivalumab, telitacicept, dazodalibep and iscalimab. Their efficacy in SjD treatment has been demonstrated by RCTs, they had not yet been approved and widely integrated into clinical practice, despite their potential for future use (107-110).

Moreover, the management of lymphomas that develop in SjD patients typically falls under the purview of hemato-oncology specialists. Therefore, despite the existence of published literature on lymphoma treatments, this guideline abstains from making recommendations on this specific topic due to the limited lymphoma treatment experience of the physicians comprising the TF.

In summary, this guideline provides a crucial set of recommendations for clinicians managing SjD, a prevalent au-

toimmune condition demanding multidisciplinary care. As the evidence base concerning SjD therapies continues to grow, a systematic and timely updating of these recommendations will be essential to maintain their clinical utility and relevance.

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