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REVIEW

Evolving treatments for Sjögren disease: current approaches and emerging targets

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Abstract

Sjögren disease (SjD) is a prevalent systemic autoimmune condition characterised by exocrine gland dysfunction, systemic inflammation and heterogeneous organ involvement. Current management remains largely symptomatic, with no approved disease-modifying therapies available and substantial unmet clinical need. However, advances in understanding immunopathogenesis have accelerated the development of targeted treatments. Ianalumab, a dual-acting B cell-activating factor receptor (BAFF) receptor inhibitor with B cell-depleting activity, is the first agent to report positive phase 3 results, showing significant improvements in systemic disease activity. Other investigational approaches include BAFF/APRIL pathway inhibition, T-cell–B-cell costimulation inhibition, type I interferon blockade, JAK–STAT, TYK2 and BTK inhibition, neonatal Fc receptor antagonist and endosomal Toll-like receptor inhibition, with exploratory modalities such as RNA-targeted agents and cellular immunotherapy (including Chimeric antigen receptor T therapy) under evaluation for severe or refractory disease. Outcome assessment has also evolved, with European Alliance of Associations for Rheumatology (EULAR) Sjögren Syndrome Disease Activity Index and EULAR Sjögren Syndrome Patient Reported Index providing validated physician- and patient-centred measures. Composite endpoints such as the Composite of Relevant Endpoints for Sjögren Syndromeand the Sjögren Tool for Assessing Response now integrate systemic, symptomatic and functional domains, improving sensitivity and feasibility in trials. Together, these tools support more rigorous evaluation of novel therapies. Overall, therapy in SjD is shifting towards precision, phenotype-informed strategies. Priorities now are confirming long-term safety and durability of response, and demonstrating patient-important benefit. In Australia, the impact of new therapies for SjD will hinge on clear diagnostic pathways, routine use of validated disease activity measures and multidisciplinary care models.

Introduction

Sjögren disease (SjD) is a chronic systemic autoimmune disease characterised by lymphocytic infiltration of exocrine glands leading to hallmark symptoms of dry eyes and/or mouth (sicca), upper airways and vagina. Beyond exocrine dysfunction, SjD often initially presents with one of a broad range of systemic manifestations such as fatigue, arthritis, cutaneous disease, interstitial lung disease (ILD) and peripheral neuropathy.[1] These systemic features not only drive substantial impairment in quality of life but also underpin major adverse outcomes, including an increased risk of lymphoma and mortality.[2]

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Treatment goals

The overarching goals of treatment in SjD are to address symptom control and improve long-term outcomes. Symptomatic management focuses on relieving sicca symptoms and alleviating pain and fatigue, which are among the most disabling aspects of the condition. At the same time, immunomodulatory treatment can limit systemic organ damage. Early detection and a multidisciplinary approach to recognise systemic involvement such as pulmonary, renal or neurological disease can prevent long-term organ damage and improve quality of life. Reducing the frequency of disease flares and minimising corticosteroid exposure are central to lowering cumulative treatment toxicity. Equally important is a patient-centred approach that acknowledges individual symptom burden, treatment goals and psychosocial needs of the patient, fostering shared decision-making and engagement of care. Ultimately, care should be coordinated by the rheumatologist who is well placed to deliver holistic management and help patients navigate the complex pathways of assessment and treatment. This involves guiding timely referral to other specialties, such as ophthalmology, dentistry and relevant areas of internal medicine, according to each patient's organ involvement, ensuring systemic manifestations are comprehensively addressed. The general practitioner plays an important role in interim care, routine health screening and optimisation of comorbidities and psychological well-being.

Current therapeutic landscape

Historically, management has centred on symptomatic therapies, with limited impact on disease course or long-term complications. Conventional disease-modifying anti-rheumatic drugs, largely adapted from rheumatoid arthritis and systemic lupus erythematosus, including hydroxychloroquine, azathioprine, mycophenolate, cyclophosphamide and methotrexate, have shown only modest and inconsistent benefit. Advances in understanding the immunopathogenesis of SjD, particularly B-cell hyperactivity, type I interferon signalling and aberrant T-cell responses, prompted evaluation of several emerging therapies that specifically target these pathways.[1] Earlier studies produced mixed outcomes, in part due to the small cohorts that were studied but also the inability to capture clinical heterogeneity and systemic disease activity.

Despite these challenges, the therapeutic landscape is evolving rapidly. The introduction of the European Alliance of Associations for Rheumatology (EULAR) Sjögren Syndrome Disease Activity Index (ESSDAI) has transformed SjD clinical trials by providing a standardised, objective measure of systemic disease activity, strengthening trial design and comparability. This is complemented by the EULAR Sjögren Syndrome Patient Reported Index (ESSPRI), a validated tool capturing patient-reported symptoms, ensuring that outcomes remain clinically meaningful (Table 1). Together these instruments have enabled more rigorous evaluation of novel therapies that target key immunopathogenic pathways.

Symptomatic glandular therapy (ocular, oral, nasal, upper airways/skin/vagina)

Management of sicca symptoms in SjD requires a multimodal, symptomatic approach tailored to the affected organ systems. For ocular involvement, first-line measures include preservative-free artificial tears, gels and night ointments to maintain lubrication. Since 2023, two formulations of topical ciclosporin eye drops have been subsidised by the Pharmaceutical Benefits Scheme in Australia for patients with severe dry eye complicated by keratitis, provided eligibility criteria are met, including evidence of keratitis on corneal fluorescein staining, an elevated ocular surface disease index and documented inadequate response to preservative-free artificial tears. Cequa is an aqueous, nanomicellar ciclosporin solution (0.09%), while Ikervis contains a cationic emulsion formulation of ciclosporin (0.1%). The efficacy and safety of Cequa and Ikervis were supported by pivotal randomised controlled studies that showed improvement as early as week 4 and may be sustained over 12 months. Topical ciclosporin acts by reducing ocular surface inflammation that contributes to tear film instability and epithelial damage, while promoting restoration of lacrimal gland function and enhancing tear production through suppression of local lymphocytic infiltration and apoptosis within the lacrimal apparatus.[3]

Additional strategies include punctal plugs to retain natural/artificial tears, and moisture chamber glasses to reduce tear evaporation, while blepharitis and meibomian gland dysfunction should be actively managed, as meibomian secretion forms an outer lipid layer of tear film that slows the rate of evaporation.[4] In addition to lid care and warm compresses, intense pulse light therapy with or without low-level light therapy has been shown to be effective for meibomian gland dysfunction.[5] Short courses of topical corticosteroids and/or topical anti-inflammatories may be considered for flares under ophthalmological supervision.

Oral manifestations are managed with sugar-free gum or lozenges to mechanically stimulate natural saliva

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Table 1 Comparison between ESSDAI and ESSPRI: two key outcomes in SjD

Feature	ESSDAI	ESSPRI
Type	Physician-assessed	Patient-reported outcome
Purpose	To measure systemic disease activity (extraglandular involvement)	To measure symptom burden (what patients feel)
Domains	Twelve domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system, haematological, biological	Three domains: dryness, fatigue, pain
Scoring	Weighted 0–3 per domain; total 0–123	Numeric rating scale (0–10) per domain; total score = mean of three items (0–10)
Strengths	Comprehensive systemic coverage: validated and reliable Used in trials and registries Defines disease activity states (e.g. low disease activity ≤4)	Simple, fast (<2 min) Directly reflects patient symptoms Captures major QoL determinants High patient acceptability
Limitations	Excludes fatigue, pain, dryness Weighting imbalance (severe single-domain can dominate) Variable responsiveness by domain Requires physician expertise (time-consuming) Dependence on laboratory tests for completion	No systemic disease coverage Limited to three symptoms (excludes depression, sleep, cognition) May not reflect organ-threatening disease
Best use	Assessing systemic activity in clinical trials and organ involvement in practice	Capturing patient-reported symptom burden and heath-related QoL impact
Complementarity	Together, ESSDAI and ESSPRI provide a dual perspective: physician-measured systemic disease versus patient-experienced symptom burden	

ESSDAI, European Alliance of Associations for Rheumatology Sjögren Syndrome Disease Activity Index; ESSPRI, European Alliance of Associations for Rheumatology Sjögren Syndrome Patient Reported Index; QoL, quality of life; SjD, Sjögren disease.

secretion, as well as saliva substitutes to provide lubrication. Secretagogues such as muscarinic receptor agonists pilocarpine and cevimeline have demonstrated efficacy in reducing xerostomia symptoms and increasing salivary flow. Pilocarpine 5 mg QID has been shown to improve symptoms of dry mouth and dry eyes and may also alleviate chronic cough due to upper airway dryness.[6] Cevimeline is another cholinergic agent with muscarinic agonist activity prominently affecting the M1 and M3 receptors prevalent in exocrine glands, and it has been shown to be effective in increasing salivary gland secretion at doses such as 30 mg TDS.[7,8]

Access to both agents remains limited, as neither is available in oral tablet form in Australia. Overseas-sourced oral pilocarpine or cevimeline can be accessed through the Therapeutic Goods Administration Special Access Scheme, although cost is often prohibitive for patients. Adverse effects of systemic pilocarpine include excessive sweating, urinary incontinence, diarrhoea, muscle weakness, airway constriction and bradycardia; thus, patients should be counselled to commence a low dose, with gradual increase to a tolerated and effective dose. In Australia, pilocarpine is primarily supplied as ophthalmic drops for glaucoma, but 4% pilocarpine eye solution can be repurposed as a topical solution for xerostomia.[8] Topical pilocarpine provides salivary stimulation comparable to systemic administration, with fewer systemic adverse effects, although dosing regimens and delivery methods have varied across studies.[8] For improved tolerability, we recommend starting with two or three drops of 4% pilocarpine eye drops in 10 mL of fluid for rinsing, e.g. using a non-alcoholic neutral pH mouthwash. Studies have reported that a solution as low as 0.01% may be effective.[9] Alternatively, the drops may be applied directly to the oral mucosa or diluted in water and swallowed, with a dose equivalent of 5 mg achieved by using two or three drops of 4% ophthalmic solution.

Longstanding dry mouth leads to gum recession, accelerated dental caries and tooth breakage, as well as increased oral infections such as candidiasis. Dental costs are significantly increased in patients with SjD, with annual costs three-fold that of average Australians.[10] Intensive dental prevention is essential, incorporating regular fluoride treatment, good oral hygiene and remineralisation agents (tooth mousse), alongside prompt treatment of oral candidiasis and management of reflux.

For nasal, skin and vaginal dryness, supportive measures play an important role in symptom control. Humidification and emollients can help relieve nasal and cutaneous dryness, while vaginal dryness requires particular attention due to its impact on sexual health, quality of life and risk of recurrent infections.[11] First-line management includes regular use of non-hormonal vaginal moisturisers and lubricants to restore comfort and reduce dyspareunia. In women without contraindications, topical vaginal oestrogen can be highly effective, improving

epithelial integrity, restoring vaginal pH and reducing the risk of recurrent candidiasis and urinary tract infections.[12] Vaginal oestrogen should be prescribed in low-dose formulations and under gynaecological or primary care guidance when long-term use is considered. Patient education and sensitive discussion of sexual health are essential to encourage adherence and to address the often underrecognised burden of vaginal dryness in SjD.

The need to recognise systemic manifestations

Recognition of systemic involvement in SjD is essential, as these manifestations frequently determine long-term outcomes. Based on the international Big Data Sjögren Project consortium analysis, a broad range of systemic manifestations has been characterised.[13] Beyond sicca symptoms, articular involvement is very common (arthralgia and myalgia, and occasionally overt synovitis and myositis; 39%–48%). Haematological features such as neutropenia and anaemia occur in 21% to 27%. Pulmonary disease, including airways disease and ILD, occurs in 9% to 20%. Less well appreciated are the breadth of cutaneous manifestations, including subacute cutaneous lupus or urticarial vasculitis (8%–16%). Other important systemic features include vasculitis (particularly cryoglobulinaemic vasculitis), renal tubular acidosis with interstitial nephritis and peripheral or cranial neuropathies (e.g. trigeminal neuralgia or facial nerve palsy). Collectively, these systemic manifestations are associated with poorer quality of life, higher treatment burden and increased lymphoma risk and mortality.

Conventional immunomodulators

Conventional immunosuppressive agents remain central to the management of systemic manifestations, with therapy tailored to organ involvement and severity. Hydroxychloroquine is recommended as baseline therapy for most patients, particularly for dryness, fatigue and skin and musculoskeletal symptoms, although efficacy data have been variable. Renewed interest in its role reflects emerging insights and potential synergy with leflunomide.[14] A small randomised trial of leflunomide plus hydroxychloroquine demonstrated a 6-month reduction in systemic disease activity compared with placebo, with manageable adverse effects (mild transaminitis and gastrointestinal upset).[15]

Methotrexate, azathioprine and mycophenolate are widely used for arthritis, cutaneous disease, cytopenia and serositis, largely supported by expert consensus and small case series. Pulmonary disease is typically managed with mycophenolate mofetil or azathioprine, often in combination with corticosteroids, following induction immunosuppression and depending on disease severity.[12] Renal involvement is managed with corticosteroids, with or without steroid-sparing agents such as azathioprine or mycophenolate, adjusted according to the severity of nephropathy. In cases of vasculitis or severe central and peripheral nervous system disease, high-dose corticosteroids combined with cyclophosphamide remain the standard for induction, with subsequent transition to maintenance immunosuppressive regimens to minimise long-term toxicity.[12]

Treatment of organ-threatening disease

For patients with organ- or life-threatening systemic manifestations of SjD, immunosuppressive therapy should be implemented promptly. High-dose glucocorticoids, with or without intravenous pulse, are the mainstay for acute severe presentations such as vasculitis, ILD, neuropathy, renal tubular acidosis with interstitial nephritis and cryoglobulinaemia. Rituximab, despite mixed results in randomised controlled trials for global endpoints, remains widely used in clinical practice and supported by current international rheumatology guidelines.[12,16] Rituximab is the first-line treatment for moderately severe cases of cryoglobulinaemic vasculitis.[17] In select cases of severe vasculitis or nonspecific interstitial pneumonia, cyclophosphamide may be used.

The more recent European Respiratory Society/EULAR guideline on connective tissue disease-associated ILD includes recommendations for SjD-associated ILD, complementing the 2021 CHEST consensus guideline from the Sjögren Foundation, which provided disease-specific guidance on the diagnosis, monitoring and treatment of pulmonary manifestations in SjD.[18,19] Immunosuppressive therapy, often in combination with glucocorticoids, is recommended. If there is progressive pulmonary fibrosis, anti-fibrotic agents such as nintedanib are also conditionally recommended. The strength of the recommendation is currently conditional, due to very few specific trials addressing SjD-ILD.

Finally, intravenous immunoglobulin (IVIg) can be considered in selected neuropathies or immune cytopaenias, providing another option for refractory cases. Current evidence is limited to case series and observational reports, but IVIg is thought to exert benefit through its immunomodulatory mechanisms by competing with pathogenic autoantibodies for binding to activating Fcγ receptors on macrophages, dendritic cells and neutrophils.[20] By saturating these receptors, IVIg reduces phagocytosis of opsonised cells and dampens downstream inflammatory signalling. Through its interaction

with inhibitory receptors (such as FcγRIIB), IVIg can also reduce B-cell receptor signalling, plasma cell survival and autoantibody production.

Biologics and targeted therapies under active evaluation

The therapeutic landscape in SjD is entering a period of rapid change, with several novel, mechanism-based agents progressing through clinical development (Table 2). Ianalumab, a B cell-activating factor receptor receptor inhibitor with antibody-dependent cellular cytotoxic B cell-depleting activity, is the first to announce positive phase 3 trial results, demonstrating significant improvements in systemic disease activity. These findings mark a potential paradigm shift and highlight the feasibility of targeted, disease-modifying therapy in Sjögren syndrome.

Close behind is dazodalibep, a novel non-antibody fusion protein that acts as a CD40L antagonist, blocking T-B costimulatory signalling (and interaction of CD40 on epithelial cells). In a phase 2 study among two distinct SjD populations, dazodalibep demonstrated improvement in ESSDAI and ESSPRI scores.[21] Other promising targets included type I interferon pathway inhibitors such as anifrolumab; JAK inhibitors, such as tofacitinib, supported by evidence of JAK-STAT activation in SjD; and deucravacitinib, a selective TYK2 inhibitor now in phase 3. Additional strategies under evaluation include FcRn inhibitors (such as nipocalimab and efgartigimod) to reduce pathogenic IgG, Bruton tyrosine kinase (BTK) inhibitors that modulate B-cell signalling and endosomal toll-like receptor antagonists targeting nucleic acid sensing. A soluble RNAse approach that dampens type 1 interferon signalling has also demonstrated improvement in fatigue and is currently in phase 2 trials. Chimeric antigen receptor (CAR)-T therapies targeting B-cell antigens, including CD19 and B cell maturation antigen, may play a role in severe, refractory SjD. While early results across other autoimmune conditions are encouraging, this approach remains experimental, and, in SjD specifically, is currently limited to early phase I trials at a small number of centres internationally, including in the United States and China. A single case report has also described symptomatic and serological improvement in a patient with SjD who received CAR-T therapy for concomitant lymphoma, supporting potential for future use of cellular therapies in this condition.

While many trials are ongoing, the overall trajectory is increasingly encouraging. Ianalumab represents an important milestone, and key questions now concern long-term safety, durability of response and patient-centred outcomes. Overall, the field is shifting from symptom control towards phenotype-informed disease-modifying treatment in SjD.

Outcome measures and composite endpoints

To standardise assessment, the ESSDAI was developed to quantify systemic activity across 12 domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral and central nervous system, haematological and biological. Domains are graded as inactive, low, moderate or high activity, with weighted scores reflecting their relative impact.[22] The ESSPRI captures patient-reported dryness, fatigue and pain. The two tools are complementary: ESSDAI reflects physician-assessed systemic involvement, whereas ESSPRI captures patient-experienced symptom burden. While concordant improvement in both systemic features and patient-reported outcomes is desirable, we recognise that in some patients there may be discordance, e.g. systemic improvement without corresponding symptomatic relief, which underscores the complexity of the disease and limitations of treatments and outcome measures (Table 1).

Composite outcome measures are essential in SjD because no single tool can capture its heterogeneous manifestations. By integrating physician- and patient-centred endpoints as well as objective measures of glandular function and B-cell hyperactivity, composite measures offer a more balanced, sensitive and discriminative assessment of therapeutic efficacy across systemic inflammation, glandular dysfunction and patient-reported symptoms. This composite focus strengthens both clinical trial design and real-world interpretation. The Composite of Relevant Endpoints for Sjögren Syndrome (CRESS) was first developed as a pragmatic and responsive composite measure, incorporating ESSDAI, ESSPRI and select biological or domain-level measures, aiming to capture clinically relevant change in a feasible way. A post-hoc analysis of phase 3 trial data demonstrated that CRESS could effectively discriminate between active treatment (abatacept) and placebo groups, with a total response rate of 65% versus 18% respectively, whereas the same phase III clinical trial did not meet its primary endpoint of ESSDAI.[23]

Later, the Sjögren Tool for Assessing Response (STAR) was developed using data-driven methods across nine randomised controlled trials and refined through international consensus, with the goal of improving composite endpoints for clinical trials.[24] STAR is designed to enhance sensitivity to change while providing a balanced evaluation of both systemic disease control and patient-reported symptom relief. A comparison between CRESS and STAR is provided in Table 3.

Table 2 Summary of emerging biologics and targeted therapies for SjD

Target/class	Drug	Mechanism of action	Summary of evidence	References
B cells	Ianalumab	B cell-activating factor receptor (BAFF-R) antagonist with dual B-cell depletion (antibody-dependent cellular cytotoxicity) and receptor blockade	First agent to show positive phase 3 results with significant improvements in systemic activity (NEPTUNUS-1/2 trials)	25,26
	Telitacicept	Transmembrane activator and CAML interactor (TACI)–Fc fusion protein, blocking BAFF and APRIL	Phase 2 study showed improved ESSDAI and good tolerability; phase 3 ongoing	27
	Nipocalimab	Fully human monoclonal antibody that binds to neonatal FcRn, reducing IgG recycling	Phase 2 RCT showed reduced IgG and improved ESSDAI; FDA fast-track designation	28
	Efgartigimod	Engineered Fc fragment designed to increase affinity for FcRn, leading to increased IgG degradation	Phase 2 RCT showed an improvement in symptoms and systemic activity using CRESS at the primary endpoint	29
Co-stimulation	Dazodalibep	CD40L antagonist	Phase 2 RCT across two distinct SjD population (high disease activity and high symptom burden groups): improvements in demonstrated improvements in systemic and symptomatic activity; phase 3 ongoing	21
Type I interferon pathway	Anifrolumab	Anti-interferon-α receptor monoclonal antibody	Phase 2 trial ongoing (ANISE-II)	30
	Deucravacitinib	TYK2 inhibitor	Ongoing POETYK SjS-1 trial, a phase 3 randomised, double-blind, placebo-controlled study	31
TLR inhibition	MHV370	Dual TLR7/8 inhibitor	Phase 2 trial ongoing; early pharmacodynamic data suggest down-regulation of interferon-inducible genes	32
Other small molecule inhibitors	Iguratimod	Broad immunomodulator (NF-κB and Th17 pathway inhibition)	Prior RCTs/meta-analysis suggest efficacy; phase 4 trials ongoing in China for Sjögren and dermatomyositis	33
	Remibrutinib	Oral BTK inhibitor	Phase 2 study with improvement in ESSDAI at week 24	34
Nuclease therapy	RSLV-132	RNase–Fc fusion protein degrading extracellular RNA	Phase 2 RCT showed reduction in interferon signature and improvement in fatigue	35

ANISE, Anifrolumab Treatment for 24 weeks in patients with primary Sjogren syndrome – efficacy and safety assessment in a randomised, double-blind, placebo-controlled phase IIa Proof-of-concept trial; APRIL, A Proliferation-Inducing ligand; BAFF, B-cell activating factor; BTK, Bruton tyrosine kinase; CAML, Calcium-modulator and cyclophilin ligand; CD40L, CD40 ligand; CRESS, Composite of Relevant Endpoints for Sjögren Syndrome; ESSDAI, EULAR Sjögren Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren Syndrome Patient Reported Index; FcRn, Fc receptor; RCT, Randomised Controlled Trial; RSLV, RNase enzyme attached to Fc portion of human IgG1; TACI, Transmembrane Activator and CAML-Interactor; TLR, Toll-like receptor; TYK2, Tyrosine kinase 2; POETYK, Phase 3 Study to evaluate the efficacy and safety of Deucravacitinib in Adults with Active Sjogren's Syndrome-1.

Table 3 Comparison between the key composite outcome measures used in SjD interventional studies

Component	CRESS	STAR
Full name of composite	Composite of Relevant Endpoints for Sjögren Syndrome	Sjögren Tool for Assessing Response
Clinical assessment	ESSDAI	ClinESSDAI
Patient-reported measures	ESSPRI	ESSPRI
Measure of lacrimal gland function	OSS	OSS
Measure of salivary gland function	UWSF or salivary gland ultrasound	UWSF

ClinESSDAI, Clinical ESSDAI; CRESS, Composite of Relevant Endpoints for Sjögren Syndrome; ESSDAI, EULAR Sjögren Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren Syndrome Patient Reported Index; OSS, Schirmer test or Ocular Staining Score; STAR, Sjögren Tool for Assessing Response; UWSF, Unstimulated Whole Salivary Flow.

Conclusion and future directions

The therapeutic landscape of SjD is moving rapidly beyond symptomatic relief towards disease-modifying strategies. Ianalumab's positive phase 3 results provide the first clear signal that targeted therapies may soon become reality. Other promising approaches, including co-stimulation blockade, FcRn inhibitors, interferon blockade and other small molecule inhibitors, are advancing through clinical trials. Nevertheless, it remains early, and important questions around safety, durability and translation into meaningful patient benefit require further clarification. The potential applications of these targeted therapies in a heterogeneous condition with complex, intersecting pathophysiological mechanisms warrant further investigation in future research and real-world trials.

In the Australian context, effective implementation will require more than therapeutic innovation. Clearer diagnostic pathways, consistent use of validated disease activity measures such as ESSDAI and ESSPRI and development of multidisciplinary models of care will be essential to ensure that advances are translated into real-world outcomes for patients.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

References

1 Baldini C, Fulvio G, La Rocca G, Ferro F. Update on the pathophysiology and treatment of primary Sjögren syndrome. *Nat Rev Rheumatol* 2024; **20**: 473–91.

2 Brito-Zerón P, Flores-Chávez A, Horváth IF, Rasmussen A, Li X, Olsson P *et al*. Mortality risk factors in primary Sjögren syndrome: a real-world, retrospective, cohort study. *EClinicalMedicine* 2023; **61**: 102062.

3 Leonardi A, Messmer EM, Labetoulle M, Amrane M, Garrigue JS, Ismail D *et al*. Efficacy and safety of 0. 1% ciclosporin a cationic emulsion in dry eye disease: a pooled analysis of two double-masked, randomised, vehicle-controlled phase III clinical studies. *Br J Ophthalmol* 2019; **103**: 125–31.

4 Balaram M, Schaumberg DA, Dana MR. Efficacy and tolerability outcomes after punctal occlusion with silicone plugs in dry eye syndrome. *Am J Ophthalmol* 2001; **131**: 30–6.

5 Park Y, Kim H, Kim S, Cho KJ. Effect of low-level light therapy in patients with dry eye: a prospective, randomized, observer-masked trial. *Sci Rep* 2022; **12**: 3575.

6 Vivino FB, Al-Hashimi I, Khan Z, LeVeque FG, Salisbury PL, Tran-Johnson TK *et al*. Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren syndrome: a randomized, placebo-controlled, fixed-dose, multicenter trial. P92-01 study group. *Arch Intern Med* 1999; **159**: 174–81.

7 Petrone D, Condemi JJ, Fife R, Gluck O, Cohen S, Dalgin P. A double-blind, randomized, placebo-controlled study of cevimeline in Sjögren's syndrome patients with xerostomia and keratoconjunctivitis sicca. *Arthritis Rheum* 2002; **46**: 748–54.

8 Kapourani A, Kontogiannopoulos KN, Barmpalexis P. A review on the role of pilocarpine on the management of xerostomia and the importance of the topical administration systems development. *Pharmaceuticals* 2022; **15**: 762.

9 Tanigawa T, Yamashita J, Sato T, Shinohara A, Shibata R, Ueda H *et al*. Efficacy and safety of pilocarpinemouthwash in elderly patients with xerostomia. *Spec Care Dentist* 2015; **35**: 164–9.

10 Lester S, Pelkas C, Kirana C, Harris J, Downie-Doyle S, Rischmueller M. Living with Sjogren's: patient perspectives. *Int J Rheum Dis* 2024; **27**: e15172.

11 Albornoz MA, Burke JF, Threlfall EK. Virgin coconut oil in paste form as treatment for dyspareunia and vaginal dryness in patients with and without rheumatic autoimmune diseases: an efficacy and safety assessment pilot study. *Cureus* 2023; **15**: e40501.

12 Price EJ, Benjamin S, Bombardieri M, Bowman S, Carty S, Ciurtin C *et al*. British Society for Rheumatology guideline on management of adult and juvenile onset Sjögren disease. *Rheumatology (Oxford)* 2025; **64**: 409–39.

13 Retamozo S, Acar-Denizli N, Rasmussen A, Horváth IF, Baldini C, Priori R *et al*. Systemic manifestations of primary Sjögren's syndrome out of the ESSDAI classification: prevalence and clinical relevance in a large international, multi-ethnic cohort of patients. *Clin Exp Rheumatol* 2019; **37** (Suppl. 118): 97–106.

14 Sandino-Bermúdez MJ, Hernández-Molina G. Hydroxychloroquine and Sjögren's disease: current evidences for its use. *Joint Bone Spine* 2025; **92**: 105799.

15 van der Heijden EHM, Blokland SLM, Hillen MR, Lopes APP, van Vliet-Moret FM, Rosenberg AJWP *et al*. Leflunomide-hydroxychloroquine combination therapy in patients with primary Sjögren's syndrome (RepurpSS-I): a placebo-controlled, double-blinded, randomised clinical trial. *Lancet Rheumatol* 2020; **2**: e260–9.

16 Ramos-Casals M, Brito-Zerón P, Bombardieri S, Bootsma H, De Vita S, Dörner T *et al*. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Ann Rheum Dis* 2020; **79**: 3–18.

17 Quartuccio L, Bortoluzzi A, Scirè CA, Marangoni A, Del Frate G, Treppo E *et al*. Management of mixed cryoglobulinemia with rituximab: evidence and consensus-based recommendations from the Italian Study Group of Cryoglobulinemia (GISC). *Clin Rheumatol* 2023; **42**: 359–70.

18 Antoniou KM, Distler O, Gheorghiu A-M, Moor CC, Vikse J, Bizymi N *et al*. ERS/EULAR clinical practice guidelines for connective tissue diseases associated interstitial lung disease. *Ann Rheum Dis* 2026; **67**: 2402533.

19 Lee AS, Scofield RH, Hammitt KM, Gupta N, Thomas DE, Moua T *et al*.

Consensus guidelines for evaluation and management of pulmonary disease in Sjögren's. *Chest* 2021; **159**: 683–98.
20 Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? *Nat Rev Immunol* 2013; **13**: 176–89.
21 St Clair EW, Baer AN, Ng WF, Noaiseh G, Baldini C, Tarrant TK *et al*. CD40 ligand antagonist dazodalibep in Sjögren's disease: a randomized, double-blinded, placebo-controlled, phase 2 trial. *Nat Med* 2024; **30**: 1583–92.
22 Seror R, Theander E, Brun JG, Ramos-Casals M, Valim V, Dörner T *et al*. Validation of EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). *Ann Rheum Dis* 2015; **74**: 859–66.
23 Arends S, de Wolff L, van Nimwegen JF, Verstappen GMPJ, Vehof J, Bombardieri M *et al*. Composite of relevant endpoints for Sjögren's syndrome (CRESS): development and validation of a novel outcome measure. *Lancet Rheumatol* 2021; **3**: e553–62.
24 Seror R, Baron G, Camus M, Cornec D, Perrodeau E, Bowman SJ *et al*. Development and preliminary validation of the Sjögren's tool for assessing response (STAR): a consensual composite score for assessing treatment effect in primary Sjögren's syndrome. *Ann Rheum Dis* 2022; **81**: 979–89.
25 Dörner T, Bowman SJ, Fox R, Mariette X, Papas A, Grader-Beck T *et al*. Safety and efficacy of Ianalumab in patients with Sjögren's disease: 52-week results from a randomized, placebo-controlled, phase 2b dose-ranging study. *Arthritis Rheumatol* 2025; **77**: 560–70.
26 Novartis announces both ianalumab phase III clinical trials met primary endpoint in patients with Sjögren's disease. 2025. Available from URL: https://www.novartis.com/news/media-releases/novartis-announces-both-ianalumab-phase-iii-clinical-trials-met-primary-endpoint-patients-sjogrens-disease
27 Xu D, Fang J, Zhang S, Huang C, Qin L, Li X *et al*. Efficacy and safety of telitacicept in primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled, phase 2 trial. *Rheumatology (Oxford)* 2024; **63**: 698–705.
28 Noaiseh G, Sivils KL, Campbell K, Idokogi J, Lo KH, Liva SG *et al*. Efficacy and safety of nipocalimab in patients with moderate-to-severe Sjögren's disease (DAHLIAS): a randomised, phase 2, placebo-controlled, double-blind trial. *Lancet* 2025; **406**: 2435–48.
29 Peene I, Verstappen GM, Deprez J, Kroese FGM, Arends S, Kelly A *et al*. OP0041 treatment of primary Sjögren's disease by blocking FcRn: clinical and translational data from RHO, a phase 2 randomized, placebo controlled, double-blind, proof-of-concept study with efgartigimod. *Ann Rheum Dis* 2025; **84**: 37.
30 ANIfrolumab treatment for 24 weeks in patients with primary Sjögren's syndrome – efficacy and safety assessment in a randomized, double-blind, placebo-controlled phase-IIa proof-of-concept trial (ANISE-II). Available from URL: https://trialsearch.who.int/Trial2.aspx?TrialID=NL%E2%80%90OMON51816
31 Fisher B, Bootsma H, Strand V, Ng W, Wegman T, Becker B *et al*. Clinical efficacy and patient-reported outcomes in anti-Ro/Sjögren's syndrome–related antigen A antibody–positive patients with active SLE treated with deucravacitinib in the Phase 2 PAISLEY Trial. *Arthritis Rheumatol* 2024; **76**. Available from URL: https://acrabstracts.org/abstract/clinical-efficacy-and-patient-reported-outcomes-in-anti-ro-sjogrens-syndrome-related-antigen-a-antibody-positive-patients-with-active-sle-treated-withdeucravacitinib-in-the-ph/
32 Alper P, Betschart C, André C, Boulay T, Cheng D, Deane J *et al*. Discovery of the TLR7/8 antagonist MHV370 for treatment of systemic autoimmune diseases. *ACS Med Chem Lett* 2023; **14**: 1054–62.
33 Pu J, Wang X, Riaz F, Zhang T, Gao R, Pan S *et al*. Effectiveness and safety of Iguratimod in treating primary Sjögren's syndrome: a systematic review and meta-analysis. *Front Pharmacol* 2021; **12**: 621208.
34 Dörner T, Kaul M, Szántó A, Tseng JC, Papas AS, Pylvaenaeinen I *et al*. Efficacy and safety of remibrutinib, a selective potent oral BTK inhibitor, in Sjögren's syndrome: results from a randomised, double-blind, placebo-controlled phase 2 trial. *Ann Rheum Dis* 2024; **83**: 360–71.
35 Posada J, Valadkhan S, Burge D, Davies K, Tarn J, Casement J *et al*. Improvement of severe fatigue following nuclease therapy in patients with primary Sjögren's syndrome: a randomized clinical trial. *Arthritis Rheumatol* 2021; **73**: 143–50.