**A viewpoint on therapeutic approaches and unmet needs in the management of young people with juvenile Sjögren's Syndrome**


## Abstract:

Juvenile Sjögren's Syndrome (JSS) is a rare disease phenotype with onset before the age of 18 years. Owning to differences in clinical presentation in children and young people compared to adults, the disease is under-recognised and under-diagnosed. Consequently, there are no evidence-based treatment and management recommendations available for patients with JSS, despite efforts to develop in the recent years, both paediatric expert-led consensus guidelines, as well as incorporate management recommendations for JSS in adult guidelines. This viewpoint highlights the potential differences in assessment strategies for children and young people compared to adults, due to differences in clinical manifestations and screening tests between JSS and adult-onset SS, as well as summarises the evidence of use and efficacy of various treatments in JSS. Better quality research is needed to evaluate the safety and efficacy of various off-label treatments used or recommended for use in patients with JSS, as well as long-term disease outcomes.


## Introduction:

It is increasingly recognised that autoimmune rheumatic diseases (ARDs) can affect people of any age, starting from early childhood and continuing until later in life. In recent decades it has become apparent that Sjögren's Syndrome (SS), commonly diagnosed in women aged 35-50 years old [1], can also affect men of all ages, as well as children and young people [2].

SS diagnosed before 18 years of age is designated as 'juvenile SS' (JSS) or 'SS with paediatric or childhood onset' and it is characterised by a less pronounced female sex bias than the adult-onset disease (F:M = 3.9-5:1 in children vs. 9-11:1 in adults) [3, 4]. More recently, a change in the nomenclature has been advocated, with the term 'Sjögren's Disease' being preferred by many clinicians and patients, and therefore potentially extrapolated to the juvenile phenotype as well [5].

In this viewpoint, we will explore the available literature related to expert opinion or evidence-based therapeutic approaches in JSS, highlighting unmet needs for better research and improved management of this rare disease phenotype. In addition, we will explore commonalities and differences between the available management recommendations for adults with SS vs. young people with JSS, to highlight potential pitfalls of extrapolating data from adults, as it is usually the case with many rare paediatric rheumatic diseases.

Despite the lack of large, good quality studies in children and adolescents with JSS overall, notable progress has been recently made in gathering multi-centre patient data, which provides evidence that clinical manifestations, especially at disease onset, differ in children and young people compared to adults with SS [3, 6, 7]. However, there is a lack of good quality evidence for safety and efficacy of various therapeutic interventions in JSS, because the disease is rare, as well as under-diagnosed and under-recognised and affecting younger populations which are less commonly involved in interventional clinical trials.

In addition, the SS classification criteria used to guide diagnosis and select homogenous adult patient populations for research purposes, perform variably in paediatric studies [4, 8, 9]. This is likely to be influenced by paediatricians' knowledge of adult SS classification criteria and their willingness to investigate children in a similar way. A survey of American paediatric

rheumatologists highlighted that only 16% and 8% reported the use of either a modified or identical version of the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria for Primary SS, respectively [10].

There are no uniformly accepted classification criteria for JSS [4, 9], therefore some studies have been using the non-validated paediatric diagnostic criteria proposed many years ago [11], while others propose new classification criteria [3].

In the context or significant literature data scarcity about the diagnosis, classification, and management of JSS, there is an unmet need to capitalise on the valuable expertise of paediatric rheumatologists and general paediatricians, as well as facilitate knowledge transfer between paediatric and adult specialists to improve data collection related to this rare disease phenotype, as well as share successful treatment approaches and resources for young patients' support.

**Aims:** In this viewpoint, we aim to explore the available evidence and recommendations for treatment of glandular and extra-glandular manifestations associated with JSS, as well as highlight the unmet needs for better research to improve JSS management. There are no good quality trials or clinical studies exploring the safety and efficacy of JSS treatments, and most therapeutic agents are used off-label as guided by clinicians' expertise in treating other paediatric autoimmune rheumatic diseases or as recommended by management guidelines for adult-onset SS. Therefore, there is a significant literature gap in exploring differences between the assessment criteria and subsequent treatment recommendations in children and young people with JSS compared to adults with SS, as well as lack of knowledge related to the natural course of the disease from childhood into adulthood to guide the best treatment decisions, which we will highlight in this viewpoint.

**Inclusion and exclusion criteria for the literature used to support this viewpoint**: As most of the published literature in JSS explores clinical and serological manifestations, as well as the role of imaging and salivary gland biopsies in diagnosing and classifying JSS rather than treatment safety and effectiveness, no strict inclusion criteria for selection of studies we refer to in this viewpoint have been applied. We have focused our discussions about therapeutic approaches used in JSS on the recent systematic review of the literature published in 2022, as well as searched for JSS studies published since then, including surveys of paediatric rheumatologists' practices relevant to JSS management to highlight the most used therapeutic options and explore the evidence regarding their efficacy. We also included published case series and case-reports to highlight current effective management strategies for refractory disease or rarer JSS manifestations. We also reviewed the current adult and paediatric treatment guidelines, to explore their commonalities and differences.

## Current consensus and evidence-based recommendations for treatment of SS across age

EULAR published in 2019 the first consensus and evidence-based management recommendations for SS [12], but like the ACR treatment guidelines published in 2017 [13], they do not include any reference to the juvenile or paediatric phenotype. Japanese paediatricians made efforts to standardise the clinical care provided to young people with JSS by publishing an updated clinical practice guidance in 2021[14], but some of the therapeutic agents and approaches suggested are not available outside Japan. The British Society of Rheumatology Sjögren's Syndrome Working Group is the first to make efforts towards publishing an integrated guideline for the management of SS across age [15].

**Challenges in establishing therapeutic recommendations specific for young people with JSS**

Although multi-centre studies in JSS have been published recently, their main focus was on reporting clinical and serological manifestations at disease onset and during early disease course when young people are followed up in paediatric centres, as well as on investigating the disease classification against validated adult criteria [3, 7, 16], with less data available on JSS management strategies. A systematic review published in 2022 found poor quality evidence for the efficacy of various treatments, mainly derived from small studies, case series and case reports [17]. A survey of American Paediatricians published by CARRA (Childhood Arthritis Research Alliance) in 2022 provided evidence that clinicians have been using various conventional and biologic disease modifying anti-rheumatic drugs (DMARDs) in their routine practice (off-label) for the treatment of recurrent parotitis or systemic manifestations associated with JSS [5], despite very poor quality evidence that these treatments work in children and adolescents [17].

In addition to the lack of good quality studies to assess the efficacy and tolerability of various treatment approaches in JSS, the natural course of the disease or the long-term risk of lymphoma (which has a 5-10% life-time risk in adults with SS) are not known. A multi-centre cohort study in JSS has been initiated in the UK/Ireland (PaedSSCoRe - Health Research Authority (hra.nhs.uk)), which aims to collect long-term data from children and adolescents with JSS through linking, wherever possible, paediatric and adult rheumatology services.

Treatment recommendations in JSS are likely to be guided by expert consensus rather than being evidence-based. In most cohort studies published in the literature, the age at disease onset is 10-14 years [2, 4, 6]. The invaluable expertise of general paediatricians and paediatric rheumatologists in managing the disease during childhood cannot fully mitigate against the challenges these patients, and their clinicians and carers, may encounter throughout their life-long disease course, especially if their disease phenotype differs from that of adult-onset SS and they are not stratified and managed according to their individual risk.

**Limitations in implementing management recommendations for adult-onset SS in JSS.**

Young people experience less dryness at disease onset, while there is evidence of increased prevalence of recurrent parotitis and systemic manifestations compared to adults with SS [2, 4, 8], thus, the disease management in childhood and adolescence is likely to be slightly different. Young people have better exocrine gland reserve overall; therefore, we do not know if strategies to preserve saliva and tear secretion should be implemented in asymptomatic or minimally symptomatic JSS patients. Clinicians previously investigated differences in SS manifestations in adults according to age at disease onset and found either no significant differences [18] or increased frequency of pulmonary manifestation in older patients, as well as increased proportion of anti-nuclear antibodies (ANA) and anti-Ro/La antibody seropositivity in younger adults with SS [19]. It is difficult to appreciate how different the JSS phenotype is later in life compared to the early or late-onset adult phenotypes, as large studies in paediatric population with long-enough follow-up are lacking.

We highlight below some of the challenges in assessing the disease severity and tailor management strategies in JSS based on the expertise available in adult-onset SS.

**Differences in management strategies in JSS vs. adult-onset SS**

Although in many ARDs with paediatric onset, treatment recommendations are made based on data derived from adult studies, there are no licensed DMARDs for use in either juvenile or adult-onset SS. Despite the significant progress made by researchers to improve personalised treatment strategies in adult SS[20] and that of the pharmaceutical industry to develop and test new therapies in adult-onset SS and the emerging evidence for their potential efficacy [21], none of the clinical trials in SS included patients younger than 18 years, or stratified patients based on their age at disease onset, making it difficult to extrapolate data from adults.

**Challenges in implementing tailored management strategies for oral dryness in JSS**

The recent EULAR management recommendations advocate for the use of an algorithm for salivary gland function assessment to guide therapeutic approaches for oral dryness in adults with SS [12], based on a 0.1ml/min cut-off for the unstimulated whole salivary flow (UWSF). However, data from literature suggest that the normal values for UWSF are much higher in healthy children and adolescents: e.g. 0.76 mL/min in children aged 6-15 years [22], making it difficult to establish if a higher cut-off should be used for younger patients with JSS or whether there is any potential benefit in supplementing or stimulating saliva secretion in young people with an UWSF above the cut-off associated with symptomatic mouth dryness in adults with SS. Similarly, the stimulated whole salivary flow (SWSF) in children seems to be characterised by higher variability than in adults. A 6-year longitudinal study in healthy children depicted two patterns of SWSF trajectory over time which led to their stratification in to a high secretion cluster of children with a SWSF cut-off value of above 1.76 mL/min and a low secretion cluster with a cut-off of 0.5 mL/min [23]. This has implications in the evaluation of children with suspected JSS, as it could significantly underestimate a potential disease-related decrease in the group characterised by a high physiological saliva secretion pattern, while the low saliva secretion group could be wrongly labelled as having moderate salivary gland dysfunction based on the interval proposed by the EULAR recommendations (0.1-0.7ml/min)[12].

The Japanese clinical guideline proposed to use the cut-off of 1.5 mL/15 min for the UWSF (closer to the cut-off proposed in adults) and 10ml/10min for the SWSF (up to 10 times higher than the cut-off used to define severe salivary gland dysfunction in adults) [14], but no clear arguments for the selection of these values were provided, suggesting the need for further research.

Other salivary gland functional tests, such as scintigraphy and sialometry or imaging techniques, such as salivary gland ultrasound are not recommended to guide oral dryness management, but they can facilitate the diagnosis of JSS in children and adolescents, especially when additional glandular pathology needs to be excluded [24, 25].

An increasing proportion (50-90%) of paediatric specialists are currently using minor salivary gland biopsies [4, 5], in addition to parotid, submandibular or even lachrymal gland biopsies [26] to facilitate JSS diagnosis and exclude other mimics. However, despite its utility for JSS diagnosis in selected cases, there is no evidence for a role of minor salivary gland biopsy in providing additional prognostic or management benefit regarding lymphoma risk in children and young people.

**Challenges in implementing tailored management strategies for ocular dryness in JSS.**

Grading and staging ocular dryness based on the quantity (Schirmer's test) and quality of tears (tear film break up time), as well as the impact of ocular dryness on the integrity of the cornea (Ocular Surface Staining - OSS), or evaluation of the patient's corneal sensitivity with impact on various activities (Ocular Surface Disease Index -OSDI) are recommended to enable

tailored management strategies to address eye dryness in adults with SS [12, 15, 27]. Although intuitively, these measures could also be implemented in children and young people, differences in the tear reserve and age-related variations in tear secretion and dry eye related symptoms reporting preclude their indiscriminate use. For example, the normal values for the tear film break-up time are greater in children aged 2-16 years, ranging from 14.9-30.95 seconds, while in adults values above 9 seconds are considered normal [28]. A meta-analysis of studies performed in children also concluded that the normal values of the Schirmer's test are different from adults [29]. Although Schirmer's test is more difficult to perform without local anaesthetic in children, the normal values found were 16.26 mm/5 min (95% CI, 13.17, 19.36) with and 29.30 mm/5 min (95% CI, 27.65, 30.96) with and without local anaesthetic, respectively. These results are different from the normal values reported in adults (10 mm/5 min), which is particularly relevant for the use of Schirmer's test as one of the classification criteria aiming to facilitate JSS diagnosis in children and adolescents.

Widely used questionnaires, such as the OSDI[30], require adapted and validated age-appropriate versions, as some questions do not apply to children (e.g. questions related to driving at night). However, other ocular measures such as the OSS, with values above 5 suggesting significant corneal involvement, are likely to provide a reliable assessment of corneal integrity in SS across age, as eye dyes can also be used in children.

**Differences in therapeutic approaches for management of dryness and glandular manifestations in JSS.**

Although most of the saliva and preservative free tear substitutes, as well as skin and vaginal moisturisers can be used across different ages, there are a few differences that need to be considered. In cases of severe oral dryness in young people, acidic saliva substitutes, such as Glandosane, are not recommended as they have detrimental demineralising effects on enamel and dentine [31]. Oestrogen-medicated vaginal moisturises are not recommended for use in young people with SS, being exclusively reserved for use in peri- and post-menopausal patients.

There are also differences in the type of ciclosporin topical preparations used for severe eye dryness in children vs. adults, because of the increased risk of local side-effects in children with certain formulations, as per local practices (e.g. in the UK, Verkazia eye drops are recommended for people younger than 18 years and Ikervis for those over 18 years, despite both containing a similar ciclosporin concentration as the tolerability is dependent of age and excipients). Homologous rather than autologous serum may be logistically more suitable for use in younger children with significant ocular dryness, especially in the context of challenging venous access.

The expertise and confidence of clinicians looking after younger patients is the key factor determining the off-label use of various medications recommended for management of SS in adults. Many of the therapeutic interventions associated with efficacy in increasing the exocrine gland secretion in adults with SS, such as pilocarpine and cevimeline [32, 33] have not been tested in patients younger than 18 years, but could be used off-license. Oral pilocarpine was beneficial in a study of young people with JSS [34]. Mucolytic agents, such as bromhexine and N-acetyl cysteine could be used from age 2, although the effective dose is not established in children.

Recurrent parotitis is one of the most frequent manifestations in JSS, and although the EULAR management recommendations [12] suggest escalation to B-cell targeted therapy with rituximab or belimumab in refractory cases based on data from available RCTs [35-37], access to biologics is likely to be limited for children and adolescents with JSS in many parts of the world, and

many of these patients are managed with oral non-steroidal and steroidal anti-inflammatory agents or glandular massage and wash-outs, while conventional and biologic DMARDs are reserved for selected cases[5].

**Management strategies for extra-glandular manifestations in JSS**

Despite the lack of licensed biologic treatments in adult SS[38], the majority of treatment decisions related to the use of conventional and biologic DMARDs in JSS are likely to be guided by the experience derived from adult SS or from other paediatric rheumatic diseases. Young people with JSS can also have overlapping disease phenotypes, similar to adults with SS[39], and in these cases, the treatment decisions are guided by their most prominent manifestations.

The management of inflammatory arthritis associated with JSS can benefit from therapeutic interventions similar to that of juvenile idiopathic arthritis, with case-reports in the literature suggesting benefit from hydroxychloroquine, methotrexate, azathioprine, sulfasalazine, etanercept, as well as short courses of glucocorticoids [17]. Skin rashes, which are common in JSS, could be managed with topical tacrolimus, providing that the treatment potency is tailored according to age (e.g. tacrolimus 0.03% topical formulation is recommended for use in patients aged 2-15 years and 0.1% concentration for people over 16 years of age).

Haematological manifestations, such as immune haemolytic anaemia and thrombocytopenia have been treated with ciclosporin and mycophenolate mofetil (MMF) [4]. Other severe manifestations, such as renal and central nervous system involvement were successfully treated with cyclophosphamide, ciclosporin, MMF, as well as rituximab, in addition to glucocorticoids [40, 41], as per experience from adult SS[42, 43]. There are very few cases of MALT lymphoma associated with JSS, but they were successfully treated with rituximab or surgical excision [44].

The most used DMARDs according to a recent evaluation of a cohort of 39 children with JSS from China were hydroxychloroquine (used in all patients) and MMF (prescribed in 58.9% patients overall and in 30.7% at the disease onset). The recent CARRA survey of paediatric rheumatologists highlighted the use of various DMARDs to address systemic manifestations in JSS, with the most prescribed medications being hydroxychloroquine, corticosteroids, methotrexate, rituximab, and MMF [5].

**Unmet needs and future research**

Despite efforts to engage the clinical community in recognising JSS as a rare disease phenotype and bring together the available expertise to facilitate research and clinical data collection, there are many unmet needs related to unanswered questions about the impact of systemic treatments, including strong immunosuppressive therapies on JSS symptoms, as well as the natural history of the disease and patients' quality of life[45]. Longitudinal studies following young patients into adulthood are lacking, therefore clinicians are not aware of the impact of available treatments on the risk of poor outcomes later in life, including the risk of malignancy and mortality. In addition, the lack of consensus classification criteria and validated outcome measures in JSS poses challenges in comparing data across cohorts, because of variable selection and assessment criteria[45]. Many young patients are still likely to experience delays in diagnosis or to be initially mislabelled as having less defined autoimmune disease phenotypes, before the hallmark symptom of SS (dryness) develops.

In addition, as there are no licensed disease modifying interventions available for adults with SS, it is difficult to appreciate if any early therapeutic intervention in childhood can significantly influence young patients' disease trajectory later in life. Treatment decisions must be balanced

against the long-term toxicity risk associated with some of the most used immunosuppressive agents. A very common practice in paediatric rheumatology is to extrapolate therapeutic recommendations based on evidence provided by adult studies, especially for treatments perceived to be associated with a lower toxicity risk, such as hydroxychloroquine. Although the level of evidence for its efficacy in controlling SS symptoms is limited [46], potential benefits of hydroxychloroquine treatment have been documented in prevention of solid organ damage associated with SS [47] and development of extra-glandular manifestations [48], aspects that are relevant for long-term outcomes of young people with JSS. Despite some methodology caveats, a recent meta-analysis of adult SS studies of hydroxychloroquine found some evidence for its efficacy in improving oral symptoms and saliva secretion, as well as serological markers, but reported no benefits for ocular dryness, fatigue or extra-glandular manifestations, which are common in both children and adults. The best quality of evidence for efficacy of hydroxychloroquine has been provided by RCTs in adult SS. However, there are challenges in extrapolating even the best quality data from adult research to JSS management, as the largest study of hydroxychloroquine in SS (JOQUER trial) did not reach its primary outcome despite a trend for improved joint pain on long term follow-up [49], while hydroxychloroquine has been unequivocally beneficial in lowering disease activity and serological markers in adults with SS as a treatment combination with leflunomide [50, 51], which is not a commonly used treatment in young people.

We would support that despite the poor level of evidence for efficacy of any of available therapeutic strategies for adult SS for children and young people with JSS, conventional and biologic DMARDs can be used off-label in selected JSS cases, as per adult recommendations [12, 27], especially in the context of severe organ involvement or refractory disease and acceptable balance of risk-benefit.

Strategies for preservation or stimulation of exocrine function are likely to be some of the most acceptable management strategies for patients with JSS, although it is difficult to advocate for their use in young patients who do not report significant dryness-related symptoms.

Future research should focus on consensus definitions in JSS, bringing together paediatric and adult rheumatologists, as well as multidisciplinary (e.g. oral medicine, dentistry, ophthalmology, general paediatrics/general medicine, gastroenterology, neurology, nephrology, specialist nursing etc.) expertise, to establish core management strategies for JSS which can be reviewed periodically as our knowledge about the disease and its impact of patients' quality of life evolves. We expect that international experts will come together to propose and validate specific and feasible classification criteria for JSS to aid the disease recognition and early diagnosis, as well as support the recruitment of homogeneous and well-defined cohorts to facilitate high quality research. Translational research can be enhanced in the future through the inclusion of SS patients of all ages (or at least of those above age 16) in interventional clinical trials to investigate novel therapeutic strategies across various disease phenotypes.

Age-tailored educational and self-management information should be designed with patients' input to support them on their disease journey, in addition to efforts to improve the disease recognition by clinicians looking after young patients across various specialties. As in many cases, JSS has potential to negatively impact at least to a certain extent the quality of life of a young individual, age-tailored self-management strategies and educational resources are needed to support patients in making decisions about JSS investigations and treatments available, in the context of current evidence about their risks and benefits. Educational and self-management resources should be directed towards equipping young patients with the

necessary tools to facilitate coping with the challenges associated with living with a long-term condition, as well as minimise the risk of development of long-term JSS complications.

**Conclusion:**

Despite the lack of good quality studies focused on the best therapeutic and management strategies in JSS, there is emerging evidence from the literature that this distinct disease phenotype requires both disease and age-tailored assessment and treatment. Further good quality research and long-term follow-up are needed to support evidence-based therapeutic recommendations specific for young people to minimise as much as possible the risk of developing irreversible organ damage and poor quality of life associated with JSS, while protecting them against the risk of potential long-term drug toxicity.

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