A Viewpoint on Therapeutic Approaches and Unmet Needs in the Management of Young People with Sjögren Disease

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Sjögren disease (SjD) in children is a rare disease phenotype, categorized with onset before the age of 18. Due to differences in clinical presentation in children and young people compared with adults, the disease is under-recognised and under-diagnosed in younger patients. Consequently, no evidence-based treatment and management recommendations are available for children with SjD, despite efforts to develop paediatric expert-led consensus guidelines in recent years and incorporate management recommendations for children in adult guidelines. This article highlights the potential differences in assessment strategies for children and young people compared with adults due to differences in clinical manifestations and screening tests between SjD in children and adult-onset SjD. Furthermore, it summarises the evidence concerning the use and efficacy of various treatments in children with SjD. Higher-quality research is needed to evaluate the safety and efficacy of various off-label treatments used or recommended for use in child patients with SjD and investigate long-term disease outcomes.

Keywords

Biologic therapies, children and adolescents, dryness, Sjögren disease in children, treatment, unmet needs

Disclosures: Coziana Ciurtin received grant funding from GSK and speaker honoraria from UCB and Novartis. Elizabeth Price has no financial or non- financial relationships or activities to declare in relation to this article

Review process: Double-blind peer review.

Compliance with ethics: This article involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the writing of this article.

Authorship: The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Access: This article is freely accessible at touchIMMUNOLOGY.com © Touch Medical Media 2024.

Received: 7 August 2023

Accepted: 29 August 2023

Published online: 19 January 2024

Citation: *touchREVIEWS in RMD.* 2024;3(1):31–36

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Support: No funding was received in the publication of this article.

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

SjD diagnosed before 18 years of age is designated as 'juvenile SjD' or 'SjD with paediatric or childhood onset', and it is characterized by a less pronounced female sex bias than the adult-onset disease (F:M is 3.9–5:1 in children versus 9–11:1 in adults).[3,4] More recently, a change in the nomenclature has been advocated, with the term 'SjD' being preferred to that of Sjögren's Syndrome by many clinicians and patients despite not being currently widely implemented in national or international guidelines.[5] In support of the newly proposed terminology, here we will refer to the juvenile disease phenotype as 'SjD in children'.

In this review, we will explore the available literature concerning expert opinion or evidence-based therapeutic approaches in children with SjD, highlighting unmet research needs and identifying ways to improve the management of this rare disease phenotype. In addition, we will explore commonalities and differences between the available management recommendations for adults with SjD versus children and young people with SjD, to highlight the 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 SjD overall, notable progress has been recently made in gathering multicentre patient data, which provide evidence that clinical manifestations, especially at disease onset, differ in children and young people compared with adults with SjD.[3,6,7] However, good-quality evidence concerning the safety and efficacy of various therapeutic interventions in SjD in children is lacking because the disease is rare, under-diagnosed and under-recognized for affecting younger populations, which are less commonly involved in interventional clinical trials.

In addition, the SjD classification criteria used to guide diagnosis and select homogenous adult patient populations for research purposes perform variably in paediatric studies.[4,8,9] This variability may be influenced by paediatricians' knowledge of adult SjD classification criteria and their willingness to investigate children in a similar way. A survey of American paediatric rheumatologists revealed that only 16% and 8% reported the use of either a modified or identical version of the 2016 American College of Rheumatology/European League Against Rheumatism (EULAR) Classification Criteria for primary SjD, respectively.[10] There are no uniformly accepted classification criteria for SjD in children.[4,9] Therefore, some studies have been using non-validated

paediatric diagnostic criteria proposed many years ago, while others propose new classification criteria.[3,11]

In the context of significant literature data scarcity about the diagnosis, classification and management of SjD in children and young people, there is an unmet need to capitalize on the valuable expertise of paediatric rheumatologists and general paediatricians. Furthermore, knowledge transfer between paediatric and adult specialists must be facilitated to improve data collection relating to this rare disease phenotype and share successful treatment approaches and resources for the support of young patients.

In this review article, we aim to explore the available evidence and recommendations for the treatment of glandular and extra-glandular manifestations associated with SjD in children and highlight the unmet needs in research to improve management of SjD in children. High-quality trials or clinical studies exploring the safety and efficacy of treatments for SjD in children are lacking, and most therapeutic agents are used off-label based on clinicians' expertise in treating other paediatric ARDs or the recommendations by management guidelines for adult-onset SjD. Therefore, there is a significant gap in the literature regarding the differences between the assessment criteria and subsequent treatment recommendations in children and young people with SjD compared with adults with SjD. Furthermore, knowledge relating to the natural course of the disease from childhood to adulthood is lacking to guide the best treatment decisions, which we will highlight in this review.

Literature used to support this viewpoint

As most of the published literature on SjD in children explores its clinical and serological manifestations, as well as the role of imaging and salivary gland biopsies in diagnosing and classifying SjD in children, rather than focusing on treatment safety and effectiveness, no strict inclusion criteria were applied to select studies we researched for this viewpoint. In our examination of therapeutic approaches employed in SjD in children, our primary emphasis is on literature published in 2022. Additionally, we searched for studies on SjD in children published since then, including surveys of paediatric rheumatologists' practices relevant to the management of SjD in children, to highlight the most used therapeutic options and to 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 manifestations of SjD in children. We further reviewed the current adult and paediatric treatment guidelines to explore their commonalities and differences. We searched the PubMed database using 'childhood or paediatric-onset Sjögren' or 'juvenile Sjögren' as well as 'parotitis in children' and 'dryness in children' as search terms.

Current consensus and evidence-based recommendations for the treatment of Sjögren disease across different age groups

In 2019, EULAR published the first consensus and evidence-based management recommendations for SjD; however, similar to the American College of Rheumatology treatment guidelines published in 2017, these recommendations do not include any reference to the juvenile or paediatric phenotype.[12,13] Japanese paediatricians made efforts to standardize the clinical care provided to young people with SjD by publishing an updated clinical practice guidance in 2021; however, some of the therapeutic agents and approaches suggested are not available outside Japan.[14] The British Society of Rheumatology Sjögren's Syndrome Working Group was the first to make efforts towards publishing an integrated guideline for the management of SjD across different age groups.[15]

Challenges in establishing therapeutic recommendations specific for young people with Sjögren disease

Although multicentre studies in children with in SjD have recently been published, their main focus has been 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, with fewer data available on management strategies for SjD in children.[3,7,16] A systematic review published in 2022 found poor-quality evidence on the efficacy of various treatments, mainly derived from small studies, case series and case reports.[17] A survey of American paediatricians published by the 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 SjD in children, despite the evidence of these treatments working in children and adolescents being poor.[5,17]

In addition to the lack of good-quality studies assessing the efficacy and tolerability of various treatment approaches in SjD in children, the natural course of the disease or the long-term risk of lymphoma, which has a 5–10% lifetime risk in adults with SjD, is not known.[18,19] A multicentre cohort study has been initiated in the UK and Ireland to collect long-term data from children and adolescents with SjD, aiming, wherever possible, to follow-up patients into adulthood[20]

Treatment recommendations in children with SjD 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 SjD and they are not stratified and managed according to their individual risk.

Limitations in implementing management recommendations for adult-onset Sjögren disease in children and young people

There is evidence that young people with SjD experience less dryness at disease onset and exhibit an increased prevalence of recurrent parotitis and systemic manifestations compared with adults with SjD.[2,4,8] Thus, disease management in childhood and adolescence is likely to be slightly different. Moreover, young people have a better exocrine gland reserve overall; therefore, we do not know if strategies to preserve saliva and tear secretion should be implemented in children with asymptomatic or minimally symptomatic SjD.[21] Clinicians previously investigated differences in SjD manifestations in adults according to age at disease onset. Their finding indicated either no significant differences in or increased frequency of pulmonary manifestation in older patients.[22] Additionally, there was an increased proportion of anti-nuclear antibodies and anti-Ro/La antibody seropositivity in younger adults with SjD.[23] It is difficult to appreciate how different the phenotype for SjD in children is later in life compared with the early- or late-onset adult phenotypes, as large studies in paediatric populations with long enough follow-up are lacking.

In the following sections, we highlight some of the challenges in assessing the disease severity and tailoring management strategies in children with SjD based on the knowledge derived from adult-onset SjD.

Differences in management strategies

Although treatment recommendations for many ARDs with paediatric onset are made based on data derived from adult studies, there are no licensed DMARDs for use in either children with SjD or adult-onset SjD. Significant progress has been made by researchers in improving personalised treatment strategies in adult-onset SjD, and considerable advancements have been made by the pharmaceutical industry to develop and test new therapies in adult-onset SjD and the emerging evidence for their potential efficacy.[24,25] Nonetheless, none of the clinical trials in SjD have included individuals 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 children with Sjögren disease

The recent EULAR management recommendations advocate the use of an algorithm for salivary gland function assessment to guide therapeutic approaches for oral dryness in adults with SjD based on a 0.1 mL/min cut-off for the unstimulated whole salivary flow (UWSF).[12] However, data from the 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).[26] These findings make it difficult to establish if a higher UWSF cut-off should be used for younger patients with SjD or whether there is any potential benefit in supplementing or stimulating saliva secretion in young people with a UWSF above the cut-off associated with symptomatic mouth dryness in adults with SjD. Similarly, the stimulated whole salivary flow (SWSF) in children seems to be characterized by higher variability than the one observed in adults. A 6-year longitudinal study in healthy children depicted two patterns of SWSF trajectory over time, which led to their stratification into 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.[27] This has implications for the evaluation of children with suspected SjD: indeed, it could significantly underestimate a potential disease-related decrease in the group characterised by a high physiological saliva secretion pattern; at the same time, the low saliva secretion group could be wrongly labelled as having moderate salivary gland dysfunction based on the interval proposed by the EULAR recommendations (0.1–0.7 mL/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 10.0 mL/10 min for the SWSF (up to 10 times higher than the cut-off used to define severe salivary gland dysfunction in adults).[14] However, no clear arguments for selecting 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; nonetheless, they can facilitate the diagnosis of SjD in children and adolescents, especially when additional glandular pathology needs to be excluded.[28,29]

An increasing proportion (50–90%) of paediatric specialists are currently using minor salivary gland biopsies, in addition to parotid, submandibular or even lachrymal gland biopsies, to facilitate diagnosis of SjD in children and exclude other mimics.[4,5,30] However, despite its utility for the diagnosis of SjD in children in selected cases, there is no evidence to support the role of minor salivary gland biopsy in providing additional prognostic or management benefits regarding the risk of lymphoma in children and young people.

Challenges in implementing tailored management strategies for ocular dryness in children with Sjögren disease

To enable tailored management strategies for addressing eye dryness in adults with SjD, the following approaches are recommended: grading and staging ocular dryness based on the quantity (Schirmer's test) and quality (tear film break up time) of tears, the impact of ocular dryness on the integrity of the cornea (Ocular Surface Staining), or the evaluation of the patient's corneal sensitivity with impact on various activities (Ocular Surface Disease Index).[12,15,31] 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 s to 30.95 s; in contrast, values above 9 s are considered normal in adults.[32] A meta-analysis of studies performed on children also concluded that the normal values for Schirmer's test are different from those observed in adults.[33] 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% confidence interval 13.17–19.36) with local anaesthesia and 29.30 mm/5 min (95% confidence interval 27.65–30.96) without local anaesthetic. These results are different from the normal values reported in adults (10 mm/5 min), which is particularly relevant in the context of using Schirmer's test as one of the classification criteria aiming to facilitate SjD diagnosis in children and adolescents.

Widely used questionnaires, such as the Ocular Surface Disease Index, require adapted and validated age-appropriate versions, as some questions do not apply to children (e.g. questions relating to driving at night).[34] However, ocular measures such as Ocular Surface Staining, where values above 5 suggest significant corneal involvement, are likely to provide a reliable assessment of corneal integrity in SjD across different age groups, as eye dyes can also be used in children.

Differences in therapeutic approaches for the management of dryness and glandular manifestations

Although most of the saliva and preservative-free tear substitutes, as well as skin and vaginal moisturizers, can be used across different age groups, there are a few differences (as detailed below) that need to be considered. In cases of severe oral dryness in young people, acidic saliva substitutes, such as Glandosane® (Fresenius Kabi Ltd, Runcorn, UK), are not recommended as they have detrimental demineralising effects on enamel and dentine.[35] Oestrogen-medicated vaginal moisturizes are not recommended for use in young people with SjD (with the expection of the ones who are oestrogen-deficient), being usually reserved for use in peri- and post-menopausal patients.

There are also differences between the type of ciclosporin topical preparations used to treat severe eye dryness in children and those employed in adults due to the increased risk of local side effects in children with certain formulations, as per local practices. For example, in the UK, Verkazia® eye drops (Santen Pharmaceutical Co., Ltd, Emeryville, CA, USA) are recommended for people younger than 18 years, and Ikervis® (Santen Pharmaceutical Co., Ltd, Osaka, Japan) 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 are the key factors determining the off-label use of various medications recommended for the management of SjD in adults. Many of the therapeutic interventions associated with efficacy in increasing the exocrine gland secretion in adults with SjD, such as pilocarpine and cevimeline, have not been tested in patients younger than 18 years, but could be used off-license.[36,37] Moreover, oral pilocarpine was found to be beneficial for the treatment of young people with SjD.[38] Mucolytic agents, such as bromhexine and N-acetyl cysteine, could be used from the age of 2, although the effective dosage has not been established for children.

Recurrent parotitis is one of the most frequent manifestations of SjD in children. Although the EULAR management recommendations for treating parotitis associated with SjD suggest escalation to B-cell targeted therapy with rituximab or belimumab in refractory cases based on data from available randomized controlled trials, access to biologics is likely to be limited for children and adolescents with SjD in many parts of the world, even if they frequently present with parotitis.[12,39–41] Furthermore, 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 children with Sjögren disease

Despite the lack of licensed biologic treatments in adult-onset SjD, the majority of treatment decisions related to the use of conventional and biologic DMARDs in children with SjD are likely to be guided by the experience derived from adult-onset SjD or from other paediatric rheumatic diseases.[42] Young people with SjD can also have overlapping disease phenotypes, mirroring the situations observed in adults with SjD.[43] In these cases, the treatment decisions are guided by the most prominent manifestations observed.

The management of inflammatory arthritis associated with children with SjD 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 and short courses of glucocorticoids.[17] Skin rashes, which are common in children with SjD, could be managed with topical tacrolimus, providing that the treatment potency is tailored according to age: for example, tacrolimus 0.03% topical formulation is recommended for use in children aged 2–15 years, and a 0.1% concentration is recommended for people over 16 years of age.[44]

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, have been successfully treated with cyclophosphamide, ciclosporin, MMF and rituximab in addition to glucocorticoids; this approach aligns with the experience gained from treating adult-onset SjD.[45–48] There have been a few cases of mucosa-associated lymphoid tissue lymphoma associated with SjD in children, but they were successfully treated with rituximab or surgical excision.[49]

According to a recent evaluation of a cohort of 39 children with SjD from China, the most used DMARDs were hydroxychloroquine (used in all patients) and MMF (prescribed in 58.9% of patients overall and in 30.7% at the disease onset).[4] The recent Childhood Arthritis Research Alliance survey of paediatric rheumatologists highlighted the use of various DMARDs to address systemic manifestations in children with SjD, with the most prescribed medications being hydroxychloroquine, corticosteroids, methotrexate, rituximab and MMF.[5]

Unmet needs and future research

Significant efforts have been made to engage the clinical community in recognising SjD in children and young people as a rare disease phenotype and bring together the available expertise to facilitate research and clinical data collection. However, many unmet needs remain in relation to unanswered questions about the impact of systemic treatments, including strong immunosuppressive therapies, on symptoms of SjD in children, as well as the natural history of the disease and patients' quality of life.[50] Longitudinal studies following young people with SjD 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 children with SjD poses challenges when comparing data across cohorts because of variable selection and assessment criteria.[50] Many children and young people with SjD 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 SjD (dryness) develops.

In addition, as no licensed disease-modifying interventions are available for adults with SjD, it is difficult to appreciate if any early therapeutic intervention in childhood can significantly influence the disease trajectory of young patients 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 SjD symptoms in children is limited, potential benefits of hydroxychloroquine treatment have been documented in the prevention of solid organ damage associated with SjD and the development of extra-glandular manifestations, aspects that are relevant for the long-term outcomes of young people with SjD.[51–53] Despite some methodology caveats, a recent meta-analysis of adult-onset SjD 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.[54] The best quality of evidence for the efficacy of hydroxychloroquine has been provided by randomized controlled trials in adult-onset SjD. However, there are challenges in extrapolating even the best quality data from adult research to management of SjD in children, as the largest study of hydroxychloroquine in SjD (the JOQUER trial; ClinicalTrials.gov identifier: NCT00632866) did not reach its primary endpoint despite a trend for improved joint pain on long term follow-up.[55] At the same time, hydroxychloroquine has been unequivocally beneficial in lowering disease activity and serological markers in adults with SjD as a treatment combination with leflunomide, which is not a commonly used treatment in young people.[56,57]

We propose that despite the poor level of evidence supporting the efficacy of any of the available therapeutic strategies for adult SjD for

children and young people with SjD, conventional and biologic DMARDs can be used off-label in selected cases of SjD in children. This aligns with adult recommendations, especially in the context of severe organ involvement or refractory disease and an acceptable balance of risk and benefit.[12,31] Strategies for the preservation or stimulation of exocrine function are likely to be some of the most acceptable management strategies for children with SjD, 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 children with SjD, bringing together paediatric and adult rheumatologists, as well as multidisciplinary expertise (e.g. oral medicine, dentistry, ophthalmology, general paediatrics/general medicine, gastroenterology, neurology, nephrology, specialist nursing), to establish core management strategies for SjD in children, 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 SjD in children and young people to aid disease recognition and early diagnosis while supporting 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 patients with SjD 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 disease recognition by clinicians looking after young patients across various specialities. In many cases, SjD in children has the potential to negatively impact, at least to a certain extent, the quality of life of a young individual; consequently, age-tailored self-management strategies and educational resources are needed to support patients in making decisions about investigations and treatments for children and young people with SjD 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 help them cope with the challenges associated with living with a long-term condition, as well as minimising the risk of development of long-term complications of SjD in children.

Conclusions

Despite the lack of good-quality studies focusing on the best therapeutic and management strategies in children with SjD, 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 minimize as much as possible the risk of developing irreversible organ damage and poor quality of life associated with SjD, while protecting them against the risk of potential long-term drug toxicity. ❑

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