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Systematic review and meta analysis

Treatment strategies for Sjögren's syndrome with childhood onset: a systematic review of the literature

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Abstract

Objectives. SS with childhood onset is a rare autoimmune disease characterized by heterogeneous presentation. The lack of validated classification criteria makes it challenging to diagnose. Evidence-based guidelines for treatment of juvenile SS are not available due to the rarity of disease and the paucity of research in this patient population. This systematic review aims to summarize and appraise the current literature focused on pharmacological strategies for management of SS with childhood onset.

Methods. PubMed and MEDLINE/Scopus databases up to December 2020 were screened for suitable reports highlighting pharmacological treatment of SS with childhood onset using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 reporting checklist. Animal studies were excluded.

Results. A total of 43 studies (34 case reports, 8 mini case series and 1 pilot study) were eligible for analysis. The studies retrieved included girls in 88% (120/137) of cases and had very low confidence levels. HCQ was prescribed for parotid swelling, as well as in association with MTX and NSAIDs in patients with arthritis and arthralgia. Corticosteroids such as long courses of oral prednisone and i.v. methylprednisolone were commonly prescribed for children with severe disease presentations. Rituximab was mainly indicated for mucosa-associated lymphoid tissue lymphoma and renal and nervous system complications. Other conventional DMARDs were prescribed in selected cases with extra-glandular manifestations.

Conclusion. Various therapies are used for the management of juvenile SS and are prescribed based on expert clinician's opinion. There are currently no good-quality studies that allow clinical recommendations for treatment of SS with childhood onset.

Key words: juvenile Sjögren's syndrome, treatment, systematic review

CLINICAL SCIENCE

Rheumatology key messages

- Sjögren's syndrome with childhood onset has heterogeneous clinical manifestations.
- There is poor-quality evidence for treatment strategies in children with Sjögren's syndrome.
- Future research is required to guide treatment recommendations in this rare disease.

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Introduction

SS is characterized by chronic lymphocytic infiltration of the exocrine glands, resulting in progressive glandular destruction, leading to mucosal dryness [1]. In children, the disease is very rare, with a prevalence that is difficult to estimate, as only a few hundred cases have been reported in the literature overall [2]. In children, SS is less well characterized in terms of clinical presentation and long-term outcomes [3]. When the disease starts before age 18 years it is called SS with childhood onset or juvenile SS. Although some recent progress in defining the disease phenotype in children has been achieved [4], SS with childhood onset remains a poorly defined and likely underrecognized and underdiagnosed condition [5]. There are also recognized overlapping clinical features with IgG4-related disease in children that frequently presents as orbital disease [6] despite evidence of distinct underlying pathogenesis [7].

There is no gold standard diagnostic tool for SS with childhood onset and therefore diagnosis is based on expert clinical opinion, which is dependent on findings from the clinical history and examination, functional exocrine gland tests, as well as serological and histological evidence [8]. Although historically the diagnostic label of 'primary SS' has been used for children [9], recent reports have highlighted the large spectrum of clinical symptoms children present with, which are difficult to map against the classification criteria for adults with primary SS [5]. Specialists also argue that it is not suitable to classify SS as 'primary' or 'secondary' to another autoimmune process, as this does not reflect the disease pathogenesis, and they propose the terminology of 'Sjögren's disease' [10]. In this article, to avoid denomination controversies, we decided to use the term 'SS with childhood onset' rather than 'primary SS in children'. Wherever children had features of other autoimmune diseases, details are provided. Therapeutic strategies are similar in children and adults, in particular because of a lack of good-quality evidence for any treatment effectiveness in children with SS, and they will be discussed below.

The purpose of this systematic literature review is to identify and analyse the main publications investigating pharmacological interventions for SS with childhood onset, with a particular focus on their clinical indication and efficacy. We also highlighted the main therapeutic trends in children and adolescents and explored differences in treatment approaches compared with adults with SS.

Methods

A full literature search was conducted using the PubMed and MEDLINE/Scopus databases to identify scientific reports that mention or discuss in detail the treatment of juvenile SS. The following search terms were used: 'juvenile Sjögren's syndrome' OR 'childhood onset Sjogren's syndrome' OR 'Sjogren's syndrome with childhood onset' OR 'Sjögren's syndrome in children' OR 'paediatric Sjögren's syndrome' OR 'recurrent parotitis' OR 'sicca in children' (PROSPERO registration ref. CRD42021251990).

Inclusion and exclusion criteria

We included original full-text articles describing randomized controlled trials (RCTs), cross-sectional studies, case series and case reports of patients with SS with childhood onset, defined as disease onset before age 18 years. We included articles published through December 2020 and excluded animal studies and abstracts.

Data extraction

Two reviewers (N.M.F. and G.D.) independently screened articles for inclusion in this systematic review. The main reasons for exclusion are recorded in Fig. 1. We grouped the information retrieved into three tables. Table 1 includes all eligible papers ($n = 43$). Tables 2 and 3 provide information on the clinical use and efficacy of all therapies used in SS with childhood onset.

Quality assessment

To assess the quality of studies, we used the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (cebm.net) (Table 1). The assessment bias was evaluated as high, as most of the studies identified were small case series and case reports, with only a very few cohort studies [11, 12].

Results

Study selection

An algorithm detailing the number of studies included and excluded, with reasons for exclusions, is included in Fig. 1. In total, 43 studies were identified as eligible. Cohen's κ coefficient for interrater agreement was 0.87 (95% agreement). Our research did not identify any interventional studies.

The papers retrieved included between 1 and 40 patients and 88% (120/127) of cases reported were girls. The patient age distribution across all eligible papers was 2.6–17 years; however, the youngest patient's age at the onset of SS symptoms was 5 months (Table 1).

Below, we present the main findings related to various therapeutic strategies used in the management of SS with childhood onset.

Evidence for use of NSAIDs

A small proportion of children with SS were prescribed NSAIDs [10% (12/118)]. From the data available for five patients, we learned that the mean age at SS diagnosis was 11 years (range 6–17) and 80% (4/5) were females. Of the 12 cases, 2 children had an overlapping diagnosis of juvenile RA (JRA) [16, 23] and another child had a diagnosis of aseptic meningoencephalitis with an old intracranial haemorrhage [14]. The main clinical

FIG. 1 Flow chart of study selection

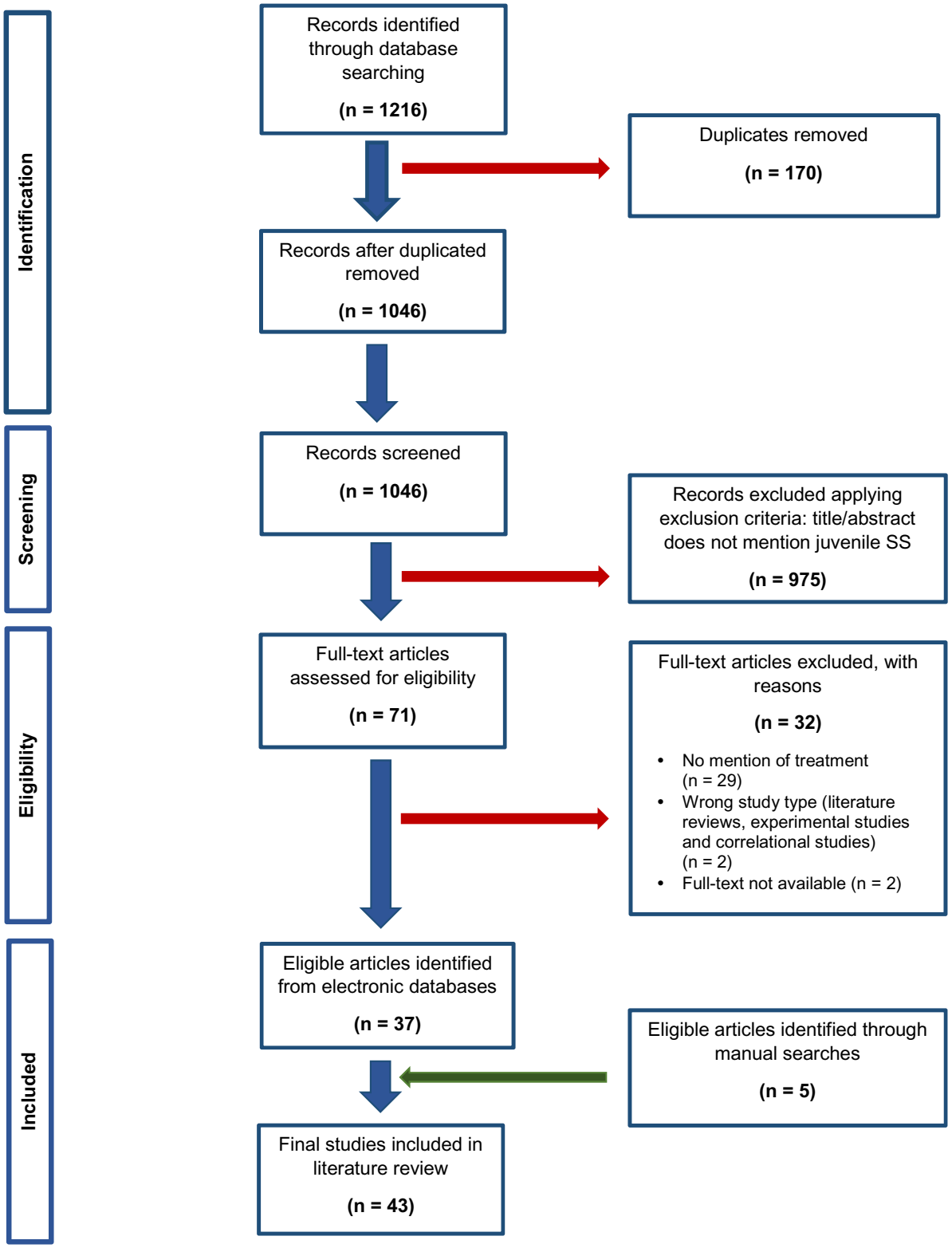


TABLE 1 Clinical manifestations and characteristics of patients with SS with childhood onset included in literature reports describing the use of various treatments

Author, year [reference]	Level of evidence (Oxford criteria)	*N* (F:M)	Patient classification criteria used	Age at symptoms onset (years)/age at diagnosis (years) [mean (range) for studies where *N* > 2]	Associated conditions/ comorbidities, *n* (%)	Cumulative signs and symptoms, *n* (%, where applicable)
Singer *et al.*, 2008 [11]	4	7 (7:0)	Not specified	NA/14.2 [10–17]	JIA, 1/7 (14)	Arthralgia, 4/7 (57) Joint swelling, 3/7 (42) Fatigue, 3/7 (42) Purpuric rash, 2/7 (29) Recurrent parotitis, 1/7 (14) RP, 1/7 (14) Headache with hemiplegia, 1/7 (14) Sicca symptoms, 1/7 (14) Mouth ulcers, 1/7 (14) Lower back pain, 1/7 (14)
Cimaz *et al.*, 2003 [12]	4	40 (35:5)	Variable classification criteria. Not specified	10.7/12.4	NA	Recurrent parotid swelling, 29/40 (75) Dry mouth, 5/40 (12.5) Dry eyes, 5/40 (12.5) Other, 5/40 (12.5) Dry eyes and dry mouth, 4/40 (10) Arthritis/arthralgia, 4/40 (10) Fever, 4/40 (10) Fatigue, 3/40 (7.5) Submandibular swelling, 2/40 (5)
Schuetz *et al.*, 2010 [13]	4	8 (7:1)	Not specified (diagnosis based on histological evidence of salivary gland involvement with or without positive autoantibodies)	6.5 [0.5–12]/10.6 [6–15]	SLE and AIH, 1/8 (12.5) JIA, 1/8 (12.5)	Arthralgia/arthritis, 4/8 (50) Systemic symptoms, 3/8 (37.5) Sicca symptoms, 3/8 (37.5) Parotitis, 3/8 (37.5) Keratitis, 2/8 (25) Renal involvement, 2/8 (25) Rash, 1/8 (12.5) Tendinitis, 1/8 (12.5) Photophobia, 1/8 (12.5) Uveitis, 1/8 (12.5) RP, 1/8 (12.5)
Kobayashi *et al.*, 1996 [14]	4	4 (4:0)	Not specified	8.75 [7–10]/10.75 [10–12]	SLE, 1/4 (25) MCTD, 1/4 (25) Interstitial nephritis, 2/4 (50) Aseptic meningoencephalitis, 1/4 (25) Thyroiditis, 1/4 (25) Intracranial haemorrhage, 1/4 (25)	Parotitis, 4/4 (100) Arthritis, 2/4 (50) Rash, 2/4 (50) KCS, 2/4 (50) Fever, 2/4 (50) Parotitis, 1/4 (25) Sicca symptoms, 1/4 (25) RP, 1/4 (25%)
Tomiita *et al.*, 2010 [15]	3B	5 (5:0)	Japanese SS diagnostic criteria (1999)	NA/13.6 [9–16]	JIA, 1/4 (25) SLE, 1/4 (25)	Xerostomia, 4/5 (80) Other symptoms not specified
Franklin *et al.*, 1986 [16]	4	5 (4:1)	At least two of the following three criteria: keratoconjunctivitis sicca, histological evidence of salivary gland involvement with SS and association with well-defined connective tissue disorder	NA/12.6 [5–17]	JRA, 4/5 (80) SLE, 2/5 (40) Proliferative glomerulonephritis, 2/5 (40) Papillary carcinoma of the thyroid gland, 1/5 (20)	Xerostomia, 5/5 (100) Xerophthalmia, 5/5 (100) Parotid enlargement, 4/5 (80) Anterior cervical adenopathy, 2/5 (40) Polyarticular arthritis, 4/5 (40)
Saad-Magalhães *et al.*, 2011 [17]	4	8 (6:2)	AECG-2002 (only 3/8 patients fulfilled the criteria)	5–13 years/NA	NA	Ocular symptoms, 5/8 (62.5) Oral symptoms, 3/8 (37.5) RP, 3/8 (37.5)

(continued)

Table 1 Continued

Author, year [reference]	Level of evidence (Oxford criteria)	*N* (F:M)	Patient classification criteria used	Age at symptoms onset (years)/age at diagnosis (years) [mean (range) for studies where *N* > 2]	Associated conditions/ comorbidities, *n* (%)	Cumulative signs and symptoms, *n* (%, where applicable)
						Recurrent parotitis, 3/8 (37.5) Arthritis, 2/8 (25) Tenosynovitis, 2/8 (25) Enlarged lymph nodes, 2/8 (25) Arthralgia, 1/8 (12.5) Myalgia, 1/8 (12.5) Osteomalacia, 1/8 (12.5) Migraine, 1/8 (12.5) Lymphocytic gastritis, 1/8 (12.5) Anaemia, 1/8 (12.5) Dry skin, 1/8 (12.5) Eczema, 1/8 (12.5) Fatigue, 1/8 (12.5) Corneal abrasions, 1/8 (12.5) Swollen parotid glands, 1/8 (12.5) Recurrent orbital swelling, 1/8 (12.5)
Hamzaoui *et al.*, 2010 [18]	4	3 (3:0)	AECG 2002	15.66 [15–16]/15.66 [15–16]	NA	Xerostomia, 3/3 (100) Parotid enlargement, 2/3 (66) Keratitis, 1/3 (33) Dental caries ,1/3 (33) RP, 1/3 (33) Arthralgia, 1/3 (33)
Yang *et al.*, 2009 [19]	4	4 (4:0)	Revised International Classification for SS (2002)	NA/9–17 years	NA	Anterior neck and axillary lymph node swellings, 2/4 (50) Haematuria and proteinuria, 2/4 (50) Repeated epistaxis, 2/4 (50) Stunted growth, 2/4 (50) Rampant caries, 2/4 (50) Arthritis, 1/4 (25) Joint swelling, 1/4 (25) Haemoptysis, 1/4 (25) Hypokalaemia, 1/4 (25) Malar rashes, 1/4 (25)
Hammett *et al.*, 2020 [20]	4	4 (4:0)	A combination of 2017 ACR/EULAR and expert opinion	16/16	N/A	Case 1: abnormal behaviour, tremors, insomnia, polyphagia, polyuria, and suicidal ideation
				16/12		Case 2: 4 year history of severe anxiety, OCD, and tic disorder presented with an abrupt and severe worsening of anxiety, OCD and new auditory hallucinations
				19/19 (adult-onset)		Case 3: progressively altered behaviour, incoherent speech, insomnia, headache, and tangential thoughts
				17/17		Case 4: new-onset suicidal ideation, paranoia, confusion and emotional lability
Pessler *et al.*, 2006 [21]	5	2 (2:0)	Expert opinion	F, 0.7/10	NA	Case 1: purpura, polyarthritis, uveitis, RTA, sialadenitis

(continued)

Table 1 Continued

Author, year [reference]	Level of evidence (Oxford criteria)	*N* (F:M)	Patient classification criteria used	Age at symptoms onset (years)/age at diagnosis (years) [mean (range) for studies where *N* > 2]	Associated conditions/ comorbidities, *n* (%)	Cumulative signs and symptoms, *n* (%, where applicable)
				F, 6/10	NA	Case 2: sialadenitis, RTA/ GN
Tesher *et al.*, 2019 [22]	5	2 (1:1)	Revised International Classification for SS (2002)	F, 15/15 M, 15/15	NA	Case 1: MALT parotid gland Case 2: MALT parotid gland, arthritis
De Souza *et al.*, 2012 [23]	5	1 (1:0)	Revised International Classification for SS (2002)	F, 8/16	NA	Dry eyes, dry mouth
Houghton *et al.*, 2005 [24]	5	2 (2:0)	Expert opinion	F, 14	NA	Case 1: parotid swelling, dental caries, keratitis, xerostomia, LIP
				F, 14		Case 2: parotid swelling
Berman *et al.*, 1990 [25]	5	1 (1:0)	Expert opinion with histological evidence (parotid biopsy)	F, 10	NMOSD, hypothyroidism	NMOSD (presented with weakness, decreased sensation in right arm, headache, dizziness, vomiting and low-grade fever)
Kornitzer *et al.*, 2016 [26]	5	1 (1:0)	Expert opinion with histological evidence (salivary gland biopsy)	F, 6/9	NMOSD	NMOSD (presented with fever, headache, progressive right-side weakness and altered mental status)
Ostuni *et al.*, 1996 [27]; specific details only given for 2 of 10 patients	4	10 (8:2)	Copenhagen criteria	11(4–14)/14.6 (11–17)	dRTA, 1/10 (10) Mesangial glomerulonephritis, 1/10 (10)	Parotid swelling, 10/10 (100) Xerostomia, 3/10 (30) Several dental caries, 1/10 (10) Rampant caries, 3/10 (30) Recurrent oral candidiasis, 1/10 (10) Other symptoms: arthralgia, fever, rash, fatigue, muscle weakness
Baszis *et al.*, 2011 [28]	4	4 (3:1)	Not specified	NA/12 [9–17]	NA	Recurrent bilateral parotitis, 3/4 (75) Unilateral parotitis, 1/4 (25) Fever, 2/4 (50) Rash, 1/4 (25) Headache, 1/4 (25) Polyarthritis, 1/4 (25)
Gmuca *et al.*, 2017 [29]	5	2 (2:0)	Expert opinion with histological evidence (lip biopsy)	F, 11	NMOSD	NMOSD (presented with optic neuritis), sicca symptoms
				F, 13		NMOSD (presented with optic neuritis)
Flaitz *et al.*, 2001 [30]	5	1 (1:0)	Expert opinion with histological evidence (labial lip biopsy)	F, 11/14	NA	Bilateral parotid swelling, dental problems
Nathavitharana *et al.*, 1995 [31]	5	1 (0:1)	Expert opinion with histological evidence (salivary gland biopsy)	M, 5	NA	Tooth decay, fever, weight loss, bilateral parotid enlargement
Siamopoulou-Mavridou *et al.*, 1989 [32]	5	2 (1:1)	Expert opinion with histological evidence (labial salivary gland and lip biopsy, respectively)	M, 8/12	NA	Recurrent parotid swelling enlargement, keratoconjunctivitis sicca
				F, 3	JRA	Arthritis, parotic gland enlargement, dry eyes and dry mouth
Civilibal *et al.*, 2007 [33]	5	1 (1:0)	Expert opinion with histological evidence (salivary gland biopsy)	F, 9/13	N/A	Recurrent bilateral swelling, arthralgia

(continued)

Table 1 Continued

Author, year [reference]	Level of evidence (Oxford criteria)	*N* (F:M)	Patient classification criteria used	Age at symptoms onset (years)/age at diagnosis (years) [mean (range) for studies where *N* > 2]	Associated conditions/ comorbidities, *n* (%)	Cumulative signs and symptoms, *n* (%, where applicable)
Pessler *et al.*, 2006 [34]	5	1 (1:0)	Expert opinion with histological evidence (salivary gland biopsy)	F, 1/11	RTA	Purpura, polyarthritis, uveitis, severe dental caries
De Oliveira *et al.*, 2011 [35]	5	1 (1:0)	American-European Consensus Group classification criteria for SS	F, 2.6	NA	Xerostomia, xeropthalmia, bilateral parotic gland enlargement
Ohlsson *et al.*, 2006 [36]	5	1 (1:0)	Expert opinion	F, 8	dRTA	Arthritis
Nikitakis *et al.*, 2003 [37]	5	1 (1:0)	Expert opinion with histological evidence (parotid biopsy and labial minor salivary glands biopsy)	F, 4	NA	Bilateral parotid gland enlargement
Ohtsuka *et al.*, 1995 [38]	5	1 (1:0)	Japanese criteria (1980–85)	F, 9	CNS manifestations	SS with CNS involvement (other symptoms included fever, nausea, xerostomia, parotid gland enlargement)
Zhang *et al.*, 2007 [39]	5	1 (1:0)	Expert opinion with histological evidence (minor salivary gland biopsy)	F, 6/9	PHTN	Recurrent parotid enlargement, xerostomia, purpura, exertional dyspnoea
Skalova *et al.*, 2008 [40]	5	1 (1:0)	Expert opinion	F, 16	dRTA	Rapid-onset muscle weakness, dysphagia, dysphonia, significant wasting
Moy *et al.*, 2014 [41]	5	1 (1:0)	Expert opinion with histological evidence (labial gland biopsy)	F, 9	NA	Recurrent parotid swelling
Ladino *et al.* 2015 [42]	5	1 (0:1)	Expert opinion with histological evidence (salivary gland biopsy)	M, 9/12	NA	Arthralgia
Thouret *et al.* 2002 [43]	5	1 (1:0)	Expert opinion with histological evidence (labial gland biopsy)	F, 9/13	NA	Bilateral parotid swelling
Shahi *et al.*, 2011 [44]	5	1 (1:0)	Expert opinion with histological evidence (salivary minor gland biopsy)	F, 10	NA	Recurrent arthralgia, foot swelling
Sardenberg *et al.*, 2010 [45]	5	1 (0:1)	Expert opinion	M, 10	NA	Recurrent parotitis, xerostomia, dental caries
Bogdanovic *et al.*, 2013 [46]	5	1 (1:0)	Expert opinion with histological evidence (kidney biopsy)	F, 13	TIN (manifested as dRTA)	Nephrocalcinosis (incidental finding), parotid gland swelling
Zhao *et al.*, 2020 [47]	5	1 (1:0)	2012 ACR criteria	F, 12	TIN	Arthritis, glucosuria
Aburiziza *et al.*, 2020 [48]	5	1 (1:0)	Expert opinion	F, 3/5	NA	Bilateral parotid gland enlargement, severe teeth decay, painful micturition
Gottfried *et al.*, 2011 [49]	5	1 (1:0)	European Classification Criteria (1996)	F, 4/9	CNS involvement	Bilateral conjunctival injection and ptosis, lip and cheek swelling, parotid gland enlargement, dry eyes and mouth

(continued)

Table 1 Continued

Author, year [reference]	Level of evidence (Oxford criteria)	*N* (F:M)	Patient classification criteria used	Age at symptoms onset (years)/age at diagnosis (years) [mean (range) for studies where *N* > 2]	Associated conditions/ comorbidities, *n* (%)	Cumulative signs and symptoms, *n* (%, where applicable)
Fidalgo *et al.*, 2016 [50]	5	1 (1:0)	Expert opinion	F, 12	JRA	Dry mouth, tooth sensitivity, dental pain, recurrent parotic gland enlargement
Majdoub *et al.*, 2017 [51]	5	1 (1:0)	Expert opinion with histological evidence (labial gland biopsy)	F, 4/7	NA	Recurrent parotid gland swelling
Vermylen *et al.*, 1985 [52]	5	1 (1:0)	Expert opinion with histological evidence (parotid gland biopsy)	F, 2/2	NA	Combination of parotid gland enlargement, hyperglobulinaemia and interstitial infiltrations of chest radiography suggestive of SS
Marino *et al.*, 2017 [53]	5	1 (0:1)	Expert opinion and evidence of cystic changes on parotid gland MRI	M, 2/1	NMOSD	Left vision loss, right hemiparesis and lethargy associated with dry mouth

AECG: American European Consensus Criteria; AIH: autoimmune hepatitis; JRA: juvenile RA; NA: not available.

indications were arthritis, asthenia and fever [13, 23, 32], and there was evidence of clinical benefit.

Evidence for use of corticosteroids in various preparations

Corticosteroids, irrespective of the dose and route of administration, were prescribed to 52% (72/137) of children with SS. From the available data, children treated with steroids had a mean age of 8.5 years at diagnosis (with an age range between 2 and 19 years) and 88% were females (38/43).

Only a small proportion of children [15% (11/72)] received i.v. methylprednisolone in combination with oral prednisone/prednisolone for various clinical indications, such as lymphocytic interstitial pneumonia (LIP) [24], central nervous system (CNS) involvement associated or not with ocular neurological manifestations [25, 29, 38, 49], SS presenting with psychiatric symptoms [20] and mucosa-associated lymphoid tissue (MALT) lymphoma [22], with overall benefit (Table 2). One patient with SS with distal renal tubular acidosis (dRTA) was treated with i.v. methylprednisolone 100 mg/day for 3 days, followed by maintenance therapy of oral methylprednisolone 4 mg every other day in combination with ciclosporin A (Table 2) [40]. Other clinical indications for oral methylprednisolone use were recurrent parotitis [52] and parotid swelling and arthralgia in combination with MTX [33] (Tables 1 and 2).

A total of 27 children (37.5%) were prescribed oral steroid treatment for JRA [16, 30, 32], tubulointerstitial nephritis (TIN) [14, 21, 46, 47], SLE [16], aseptic meningoencephalitis [14], severe isolated pulmonary hypertension (PH) [39], dRTA [46], mesangial glomerulonephritis [27], parotitis [11, 28, 30, 31, 48] or orbital swelling [17] (Tables 2 and 3).

The response to oral steroid treatment was only described in 14/27 of these patients and all reported clinical improvement, which is difficult to attribute to steroids alone, as some patients were treated with additional DMARDs (Tables 2 and 3).

Evidence for use of conventional DMARDS

Based on the available data, 85/137 (62%) children with SS were treated with DMARDs (conventional and biologic).

HCQ

HCQ treatment was prescribed in 34% of children with SS (46/137) (Table 2); 68% were girls and had a mean age at diagnosis of 13 years (range 7–17). Some children had overlapping phenotypes, including SLE and JIA (Table 2).

The most frequent clinical indications for HCQ were unilateral or bilateral parotid swelling in 15% (7/46) of children [28, 41, 43, 51], arthralgia [4.3% (2/46)] [18, 44], renal involvement [4.3% (2/46)] [27] and a combination of arthralgia and fatigue [2% (1/46)] [42] (Table 2). HCQ was also prescribed as maintenance therapy for SS presenting with psychiatric symptoms [2% (1/46)] (Table 3). In a large proportion of reports [72% of patients (33/46)] the symptoms/signs targeted by HCQ treatment were not mentioned. The doses prescribed varied from 200 to 400 mg/day.

The response to HCQ treatment was favourable in 39% (18/46) of children (Table 2). Because HCQ was used in combination therapy, either with Celebrex, SSZ, prednisone, naproxen, AZA, rituximab (RTX) or bendamustine, it is difficult to attribute the clinical improvement to treatment with HCQ alone. The reports also identified a lack of improvement or side effects from HCQ in 15% (7/46) of children with SS (e.g. worsened

Table 2 Evidence of efficacy for the use of NSAIDs, corticosteroids, HCQ and topical treatments in SS with childhood onset

Treatment	Reference	Acute symptoms/signs associated with SS targeted by treatment	Response	Background medications	Symptoms/signs targeted by background medications	Response
NSAIDs	Kobayashi *et al.*, 1996 [14]	Secondary SS to mixed connective tissue disease, no details of symptoms targeted by treatment	No clear benefit or further details. Liver functions remained abnormal	NA	NA	NA
	De Souza *et al.*, 2012 [23]	Arthritis, parotitis	Controlled arthritis with no systemic evolution of SS after a 12 month follow-up. No further parotitis episodes	NA	NA	NA
Oral corticosteroids	Schuetz *et al.*, 2010 [13]	Sicca syndrome, fever, abdominal pain, parotid swelling	Good response	NA	NA	NA
	Houghton *et al.*, 2005 [24]	LIP	Clinical and radiographic improvement	HCQ	Not specified	Not specified
	Flaitz *et al.*, 2001 [30]	Parotitis and fever	Cessation of pyrexia, decrease in size of parotid gland swelling and improved appetite. Two months after treatment, there was evidence of improvement in non-specific markers of inflammation but hypergammaglobulinemia persisted	NA	NA	NA
	Nathavitharana *et al.*, 1995 [31]	Parotitis	Evidence of clinical improvement after 2 months of treatment	Not specified	Rampant caries	Not specified
	Saad-Magalhães *et al.*, 2011 [17]	Recurrent orbital swelling	Prompt response	NA	NA	NA
	Yang *et al.*, 2009 [19]	Kidney involvement	Relieved symptoms (non-specific)	NA	NA	NA
	Siamopoulou-Mavridou *et al.*, 1989 [32]	Juvenile RA and SS	Evidence of clinical improvement after 2 months	Aspirin 90 mg/kg/day	Not specified	Not specified
	Civilibal *et al.*, 2007 [33]	Parotid swelling, arthralgias, local oedema and purpura	Follow-up at 6 months: patient reported only one parotid swelling attack; arthralgias, local oedema and purpura disappeared completely	MTX 10 mg/m^2/week	Same symptoms	Improvement, as mentioned

(continued)

Table 2 Continued

Treatment	Reference	Acute symptoms/signs associated with SS targeted by treatment	Response	Background medications	Symptoms/signs targeted by background medications	Response
	Zhao *et al.*, 2020 [47]	Tubular interstitial damage	Treatment with prednisone (5–10 mg/day) for half a year (for persistent renal glycosuria). At 1.5 years follow-up there was stable renal function	Celebrex (200 mg/day) and HCQ (100 mg/day) for the first week. HCQ (200 mg/day) and SSZ enteric-coated tablets (400 mg/day) for the next 6 months	Joint pain, increased ESR	Complete remission of joint pain, normal complete blood counts and ESR at 2 months follow-up
	Kobayashi *et al.*, 1996 [14]	Primary SS. Presented with aseptic meningoencephalitis	Symptoms resolved and condition has been stable on low-dose prednisolone (5 mg/day)	Acetylsalicylic acid, diclofenac	High-grade fever, headache, nausea and skin rash	Symptoms resolved
Methylprednisolone i.v.	Kobayashi *et al.*, 1996 [14]	Primary SS complicated with overt dRTA	Good response to treatment. Patient's condition and renal function have remained stable during 5 years of follow-up	CYC, sodium citrate	Same symptoms	Good overall response
	Houghton *et al.*, 2005 [24]	LIP	Clinical and radiographic improvement	3 daily pulses of i.v. methylprednisolone (1 g/day) followed by prednisone (1 mg/kg/day), additional HCQ	Same symptoms	Clinical and radiographic improvement
	Ohtsuka *et al.*, 1995 [38]	CNS involvement: hemiparesis, diffuse swelling of the cervical cord and increased signal intensity on MRI	Resolution of symptoms occurred progressively after i.v. methylprednisolone	Corticosteroids for 28 days; prednisolone (2 mg/kg/day then tapered to 0.2 mg/kg/day), followed by i.v. methylprednisolone 30 mg/kg/day for 3 days	Same symptoms	Four months after being discharged from hospital, patient developed nausea, headache and new-onset left hemiparesis despite being on prednisolone (0.2 mg/kg/day), requiring i.v. methylprednisolone
	Gottfried *et al.*, 2011 [49]	Orofacial swelling, facial nerve palsy or stroke-like symptoms	Rapid improvement of diplopia, disequilibrium and ataxia, less prominent ptosis while facial diplegia remain unchanged after i.v. methylprednisolone therapy	Oral prednisolone (2 mg/kg/day) then slowly tapered over the next 3 months following i.v. methylprednisolone for 5 days	Same symptoms	MRI showed full resolution of midbrain lesion at a the 6 month follow-up. Patient continued to improve with full conjugate extraocular movements, minimal ptosis and stable facial diplegia
HCQ	Schuetz *et al.*, 2010 [13]	Not specified	2/3 (66.6%) clinically stable, 1/3 (33.3%) not specified (patient later diagnosed	1/3 steroids 1/3 NSAIDs	Arthritis and "skin eruption," asthenia, fever, arthritis of toes and forefeet	Good response. Controlled symptoms for 1 year until development of asthenia and

(continued)

Table 2 Continued

Treatment	Reference	Acute symptoms/signs associated with SS targeted by treatment	Response	Background medications	Symptoms/signs targeted by background medications	Response
			with SS with overlapping SLE and started on AZA)			jaundice—diagnosed with AIH with underlying diagnosis of SS with overlapping SLE. Responded partially to NSAIDs
	Moy *et al.* 2014 [41]	Parotitis	Patient still had recurrent bilateral/unilateral parotid swelling in the subsequent 3 years despite HCQ therapy	Antibiotics	Episodes of parotitis lasting 1 week were treated with antibiotics	Still recurrent symptoms
	Hamzaoui *et al.*, 2010 [18]	Inflammatory arthralgia	Good	NA	NA	NA
	Ladino *et al.*, 2015 [42]	Joint pain and fatigue	Prednisone and HCQ associated with good response in terms of joint pain and fatigue	Prednisolone (7.5 mg/day), artificial tears, oral mucolytic	Eye dryness, xerostomia	Artificial tears associated with benefit for eye dryness, oral mucolytic treatment beneficial for xerostomia
	Thouret *et al.*, 2002 [43]	Parotid swelling	Clinical improvement of bilateral parotid swelling, although no impact on serological markers	NA	NA	NA
	Shahi *et al.*, 2011 [44]	Recurrent arthralgia	Stable clinical features and laboratory values at 6 months follow-up. No mention of response to HCQ therapy	A	N/A	NA
	Majdoub *et al.*, 2017 [51]	Parotid swelling	HCQ was effective in preventing parotid swelling (at 2 year follow-up, no flares were reported since starting HCQ)	Artificial tears	Dry eyes	Effective
Treatments for dryness-related symptoms						
Pilocarpine	Tomiita *et al.*, 2010 [15]	Xerostomia	Improved in 5/5 (100%) patients. Specified as 'improved' in 1/5 (20%), 'slightly improved' in 4/5 (80%)	NA	NA	NA

(continued)

Table 2 Continued

Treatment	Reference	Acute symptoms/signs associated with SS targeted by treatment	Response	Background medications	Symptoms/signs targeted by background medications	Response
	De Souza *et al.*, 2012 [23]	Dryness	Adequate control of SS symptoms	NA	NA	NA
Bromhexine	Hamzaoui *et al.*, 2010 [18]	Dryness	Not specified	NA	NA	NA
Artificial tears	Hamzaoui *et al.*, 2010 [18]	Eye dryness	Not specified	NA	NA	NA
Oral balance gel	Nikitakis *et al.*, 2003 [37]	Xerostomia	No new cavities at 10 months follow-up	NA	No systemic symptoms	Stable clinical features and laboratory values with no evidence of connective tissue disease
Plaque control, diet modification, regular fluoride application, restorative treatment	Sardenberg *et al.*, 2010 [45]	Xerostomia and dental problems	No complications or new carious lesions at 2 year follow-up	NA	NA	NA
Oral hygiene instructions, vulvar moisturizer, 1% hydrocortisone cream for intermittent use	Aburiziza *et al.* 2020 [48]	Dental problems, vulvar dryness	Patient continued to have new dental caries. Vulvar itchiness and irritation became a prominent clinical problem 2 years after presentation	Short course of oral prednisolone given once with antibiotics	Parotitis	Resolved
Artificial saliva, dental treatment	Fidalgo *et al.*, 2016 [50]	Dry mouth, tooth sensibility and dental pain	Artificial saliva: improved hydration of the tissues of the oral cavity, in particular the oral mucosa. Successful endodontic treatment and dental restorations	Corticoid therapy	Additional diagnosis of RA, parotitis	No details

AIH: autoimmune hepatitis; NA: not available.

Table 3 Evidence of efficacy for the use of conventional and biologic DMARDs in SS with childhood onset

Treatment	Reference	Acute symptoms/signs associated with SS targeted by treatment	Response	Background medications	Symptoms/signs targeted by background medications	Response
MTX	Hamzaoui *et al.*, 2010 [18]	Arthritis	Excellent response. Stopped following diagnosis of SS and maintained on low-dose corticosteroids	Low-dose corticosteroids	Uveitis, maintenance (following MTX)	Good control. Clinically stable
	De Oliveira *et al.* 2011 [35]	Myalgia and arthralgia (very low dose 2.5 mg weekly associated with oral methylprednisolone)	No mention of treatment response for methylprednisolone and MTX	Oral methylprednisolone 9 mg every 48 h. 1% neutral sodium fluoride every 3 months since diagnosis	Myalgia and arthralgia, oral dryness	At 6 year follow-up, patient has well-controlled oral health
	Ohlsson *et al.*, 2006 [36]	Arthritis, dRTA	No details provided	HCQ. No further information on treatments	NA	NA
	Civilibal *et al.*, 2007 [33]	Severe arthralgia	Symptoms resolved at 6 month follow-up	Methylprednisolone (1 mg/kg/day)	Local oedema and purpura, bilateral parotid swelling	6 months after discharge the patient had only one episode of parotid swelling; local oedema and purpura disappeared completely
MMF	Pessler *et al.*, 2006 [21]	Primary SS complicated with overt dRTA	No mention of treatment response	Electrolyte supplementation	Same manifestations	Not available
CYC	Berman *et al.*, 1990 [25]	Optic neuropathy and CNS involvement associated with primary SS	Visual acuity improved. Patient stable with no new cerebral infarcts	Oral corticosteroids followed by i.v. steroids in combination with i.v. CYC therapy	Same manifestations	As mentioned
	Gmuca *et al.*, 2017 [29]	NMOSD	No mention of treatment response in case 1. Visual symptoms worsened in case 2 following treatment and thus the patient received apheresis and RTX	Case 1: i.v. methylprednisolone, RTX in association with CYC, apheresis Case 2: HCQ, i.v. methylprednisolone, CYC, switched to mycophenolate as maintenance	Same manifestations	As mentioned
	Zhang *et al.*, 2007 [39]	SS associated with pulmonary hypertension	At 1 month follow-up, exertional dyspnoea improved dramatically (assessed by walk test). Patient remained stable after prednisolone was tapered and diltiazem was stopped	Prednisolone (0.5 mg/kg/day then gradually tapered), diltiazem, anticoagulant therapy	Same manifestations	As mentioned

(continued)

Table 3 Continued

Treatment	Reference	Acute symptoms/signs associated with SS targeted by treatment	Response	Background medications	Symptoms/signs targeted by background medications	Response
	Kobayashi *et al.*, 1996 [14]	SS secondary to SLE, membranous and mesangial glomerulonephritis (lupus nephritis class 2, 3) and interstitial nephritis	Good response to treatment; 24 h urinary excretion of protein decreased. Patient's condition and renal function remained stable during 7 years of follow-up	Methylprednisolone orally followed by prednisolone orally	Initially presented with arthralgia, RP, sicca symptoms, photophobia, facial rash and recurrent parotitis	Good response. Sicca symptoms resolved without using artificial tear or saliva
Ciclosporin	Skalova *et al.*, 2008 [40]	SS associated with hypokalaemia paralysis	Good response	Methylprednisolone (4 mg every other day), potassium chloride (2.5 g/day), Shohl's solution (9 ml twice daily)	Same manifestations	As mentioned
AZA	Bogdanovic *et al.*, 2013 [46]	dRTA/TIN	Significant improvement at 6 months follow-up	Potassium citrate (for dRTA), prednisone (1 mg/kg/day) for 6 months then tapered to 0.5–0.25 mg/kg/day (for TIN). After 3.5 years, MMF replaced AZA for several months	Same manifestations	At 6 years follow-up there was no evidence of xerostomia, xerophthalmia or any other SS-related symptoms
	Singer *et al.*, 2008 [11]	SS overlapping with SLE with autoimmune hepatitis	Improvement	HCQ	Not specified	Not specified
Biologic treatments						
IVIG	Hamzaoui *et al.*, 2010 [18]	Hepatitis, myositis, pericarditis, oral dryness	Clinically stable	Corticosteroids (short course)	Not specified	Not specified
Etanercept	Pessler *et al.*, 2006 [21]	Arthritis	At the 4 year follow-up, arthritis responded well to etanercept (disappearance of tender and swollen joints)	HCQ (200 mg daily), MTX (25 mg s.c. weekly)	Renal tubular dysfunction	Normal urinalyses and serum creatinine levels but unchanged renal tubular dysfunction (evidenced by stable requirements for oral sodium citrate (3 mEq/kg/24 h), potassium (3 mEq/kg/24 h) and phosphate supplementation)
Infliximab switched to etanercept because of loss of response	Pessler *et al.*, 2006 [34] (likely the same case as reported in the paper above)	Chronic polyarthritis	Initial good response to infliximab, loss of response after 7 months despite dose increase and	NSAIDs, corticosteroids, MTX (0.5 mg/kg once weekly s.c.) and topical steroid eye drops	Xerostomia, uveitis, optic neuritis, RTA	Systemic symptoms developed during treatment with infliximab and not influenced by

(continued)

Table 3 Continued

Treatment	Reference	Acute symptoms/signs associated with SS targeted by treatment	Response	Background medications	Symptoms/signs targeted by background medications	Response
			3 weeks of infliximab administration. Good response to etanercept after 18 months	for presumed JRA with uveitis		subsequent treatment with etanercept
Rituximab	Tesher *et al.*, 2019 [22]	MALT lymphoma	Both patients achieved remission of MALT lymphoma, with one case having no recurrence of symptoms associated with SS at the 2 year follow-up	Case 1: additional pulsed 1 g i.v. methylprednisolone, HCQ daily Case 2: parotidectomy; bendamustine after a course of RTX (due to anaphylaxis to RTX) followed by HCQ monotherapy	Medication mainly targeted at MALT	As mentioned
	Kornitzer *et al.*, 2016 [26]	NMOSD	Clinically improved but not clear if this was related to RTX treatment. Only residual subtle right-sided weakness and mild abducens and facial nerve weakness on examination 3 years after presentation	NA	NA	NA
	Hammett *et al.*, 2020 [20]	Psychosis	Psychiatric symptoms improved with RTX infusions in all four patients (at 4–6 month intervals). One patient allergic to RTX was switched to obinutuzumab with maintained benefit	Case 1: pulse methylprednisolone 1000 mg daily for 3 days followed by a prednisone taper over 24 weeks, olanzapine Case 2: aripiprazole and obinutuzumab, as the patient developed an allergic reaction to RTX Case 3: MMF 1500 mg twice a day, oral prednisone 2.5 mg/day, risperidone along with benztropine and clonazepam Case 4: pulse methylprednisolone for 3 days followed by	Various psychiatric manifestations including: insomnia; increase in hallucinations, tics and anxiety after starting an oral contraceptive; catatonia; suicidal ideation; fluctuating coherence; delusions; slow psychomotor responses and echolalia, echopraxia and posturing	All patients improved and were able to go back to a normal life

(continued)

Table 3 Continued

Treatment	Reference	Acute symptoms/signs associated with SS targeted by treatment	Response	Background medications	Symptoms/signs targeted by background medications	Response
Tocilizumab	Marino *et al.*, 2017 [53]	NMOSD	Neurological manifestations: left vision loss, right hemiparesis and lethargy not well controlled by RTX and i.v. methylprednisolone	oral prednisone taper, HCQ 200 mg daily No concomitant medication. Previous treatment with CYC and RTX followed by MMF. Despite complete depletion of $CD19^+$ B lymphocytes, the patient continued flaring	Same manifestations	Clinical remission

AIH: autoimmune hepatitis; NA: not available.

visual symptoms [29], hypersensitivity [11], recurrence of parotitis [28] or a lack of clinical benefit [11, 41]). However, data on HCQ efficacy were lacking in 32% (15/46) of children.

MTX

MTX was prescribed in 5.8% (8/137) of children with SS. The mean age at SS diagnosis was 10 years (range 2–17) with an equal distribution of sexes (4 females, 4 males).

Among this small number of children treated with MTX, 25% (2/8) had an overlapping diagnosis of JIA [11, 13] and 25% (2/8) presented with RTA at disease onset [21, 36]. The main clinical indications were arthralgia and purpura [33, 35], polyarthritis [21] and JIA [11]. The weekly MTX dose varied from 2.5 mg (age 2 years 7 months) [35] to 10 mg/m^2 (age 13 years) [33] to 25 mg once a week (age 10 years) [21]. Where reported (4/8 patients), MTX was associated with clinical benefit.

AZA

Only a very small proportion of children with SS [2% (3/137)] were prescribed AZA. All three patients were female with an average age at SS diagnosis of 15 years [13, 14, 16, 23, 32]. The clinical indications were overlapping JIA and SLE with autoimmune hepatitis phenotypes [11, 13] as well as TIN, in which case AZA was used as the initial therapy, followed by MMF after a loss of efficacy [46].

CYC

Nine girls with a mean age at SS diagnosis of 11.5 years [9–14, 16, 23, 32] were treated with CYC for a diagnosis of TIN [14, 21], neuromyelitis optica spectrum disorder (NMOSD) [29], isolated PH [39], SS presenting with psychiatric symptoms [20] or CNS involvement associated with thyroiditis [25]. The most detailed case was that of a 9-year-old girl with symptoms onset at age 6 years, who experienced recurrent parotid enlargement, xerostomia, purpura and exertional dyspnoea and was eventually diagnosed as severe isolated PH associated with SS based on clinical manifestations, hyperglobulinemia, positive ANA, SSA and SSB and an abnormal Schirmer test (Table 3). The patient received CYC at a dose of 100 mg every other day alongside prednisolone, diltiazem and anticoagulant therapy with significant improvement [39].

MMF

MMF was used to treat four patients with SS and an additional diagnosis of NMOSD [29] or TIN [46] or as maintenance therapy for severe renal involvement evident on biopsy [21] (Table 3). MMF was also given as maintenance therapy in combination with RTX for one patient with SS manifesting with psychiatric symptoms, with good response [20].

Ciclosporin A

Ciclosporin A was given to three patients but a favourable response to treatment was only documented in one

case report of a 16-year-old female with a diagnosis of SS with dRTA [40].

SSZ

One female patient, age 12 years, was prescribed SSZ 400 mg/day in combination with HCQ for arthritis associated with SS and achieved remission of joint pain after 2 months of treatment [47].

Evidence for use of biologic DMARDs

Biologic treatments such as RTX and etanercept or infliximab were prescribed in a minority of patients. Of the nine patients that were prescribed RTX, two patients had a diagnosis of MALT lymphoma [22], three patients had NMOSD [26, 29] and four adolescent patients had SS presenting with severe psychiatric symptoms [20].

One patient (female, age 15 years) who was diagnosed with MALT lymphoma achieved remission of >3 years following four 375 mg/m^2 once-weekly doses of RTX, alongside pulsed i.v. methylprednisolone and regular HCQ at a dose of 200 mg/day [22], while another patient reported an anaphylactic reaction with the second RTX infusion [22] (Table 3). Both patients (a boy and a girl) had parotid gland involvement and were diagnosed at age 15 years. The boy had additional features of arthritis and was treated with parotidectomy and bendamustine after a course with RTX associated with anaphylaxis; he was discharged on HCQ monotherapy. The girl received additional treatment with i.v. methylprednisolone and HCQ daily. Both patients achieved remission of MALT lymphoma (Table 3).

There is no mention of response to RTX in two cases of NMOSD [29], while good clinical outcome was reported in the third case [26] (Table 3). Of the four patients who were given RTX for SS with psychiatric involvement, three patients experienced significant improvement in symptoms and were able to be weaned off antipsychotics [20]. RTX was discontinued in the remaining patient due to the development of RTX-induced serum sickness and obinutuzumab was commenced as an alternative, with good response [20].

Treatment with etanercept was initiated in one child with SS and juvenile arthritis was reported extensively in the literature [11, 21, 34] and was associated with clinical benefit (Table 3).

Other immunomodulatory therapies

Intravenous immunoglobulin (IVIG) was successfully prescribed for indications such as hepatitis, myositis, pericarditis and oral dryness in one patient [13] and was also given in combination with steroids and MTX to treat CNS manifestations in another patient with good clinical outcomes [11].

There was also evidence of therapeutic success with tocilizumab in a boy with neurological manifestations compatible with NMOSD (left vision loss, right hemiparesis and lethargy) who was subsequently diagnosed with SS at age 14 years based on a combination of dry mouth, positive serology and the presence of parotid cysts on MRI [53]. Treatment with tocilizumab was initiated after four courses of RTX and i.v. methylprednisolone over 2 years that were not successful in controlling neurological relapses. Treatment with tocilizumab was associated with no further relapses after 3 years.

Evidence for use of topical treatments and other therapies for oral dryness

A total of 17 of 137 children (12.4%) were prescribed treatments for their oral sicca symptoms. Their mean age at SS diagnosis was 11.5 years [2–14, 16, 23] and 76% (13/17) were females.

A significant proportion of children [35% (6/17)] were prescribed oral pilocarpine as treatment for their oral sicca symptoms [15, 23]. There was evidence of clinical benefit in all patients.

Other treatments were also prescribed for oral symptoms or as prophylactic treatment against dental caries, ranging from bromhexine [18], sodium fluoride topical treatment for enamel protection [35, 45], fluoride varnish for dental caries [31], artificial saliva [37, 50] and oral mucolytic treatment [42], with evidence of overall benefit, with the exception of oral bromhexine, for which the outcome of treatment was not specified [18].

Evidence for use of topical treatments and other therapies for ocular symptoms

A total of 19% (26/137) of children were prescribed treatments for their ocular sicca symptoms. Data about the patients' ages were retrievable in 81% (21/26) of children: the mean age at SS diagnosis was 13 years (range 7–17) and 77% (20/26) were females. The most used therapeutic interventions for eye dryness were humidifier eye drops [17], artificial tears [18, 22, 27, 28, 32, 42, 51] and topical lubricants [25, 28], however, the response to treatment was not specified in the majority of cases.

Conclusion

This methodologically robust systematic review of the literature demonstrates that there is currently no standardized treatment regime for childhood-onset SS and that the therapeutic decisions are based on clinicians' expertise and preference and very likely derived from adult SS studies. In addition, there are no validated disease activity outcome measures for use in children with SS, thus the response to treatment was assessed based entirely on clinician opinion.

The British Society for Rheumatology (BSR) guidelines for the management of adults with SS [54] recommend a few general strategies for treatment, including conservation of oral and ocular secretions and replacement of tears and saliva, therapies for stimulating oral and ocular secretions (including pilocarpine, cevimeline and nizatidine) and treatment of severe ocular complications (topical ciclosporin) and glandular swelling (short courses of oral steroids or i.m. depomedrone). Corticosteroids, including pulse therapy, are recommended for lung, haematological, renal and neurological manifestations in combination with other DMARDs, while low-dose oral

prednisolone (5–7.5 mg/day) could provide a modest benefit for sicca symptoms.

HCQ is recommended as the first-line treatment in adults with systemic disease manifestations, specifically skin disease, joint disease or fatigue [54]; MTX for inflammatory arthritis; AZA for lung disease, myelopathy and cytopaenia; and MMF for lung disease and cytopaenia, while CYC may be considered in patients with organ-threatening systemic complications such as CNS, renal or lung disease. The BSR guidelines recommend the use of RTX in patients with systemic disease manifestations refractory to other immunosuppressant agents and in those with particular manifestations such as lymphoma, immune thrombocytopenia, vasculitic neuropathy or cryoglobulinaemia [54]. There is no current evidence to suggest RTX efficacy in the treatment of sicca symptoms and non-specific symptoms including fatigue [55].

The most frequently used treatments in children with SS were corticosteroids, HCQ and NSAIDs, with conventional and biologic DMARDs being reserved for selected cases. From the 43 studies that were included in this systematic literature review, a few general therapeutic trends emerged.

HCQ was predominantly used to treat parotid swelling and as a background treatment for other manifestations such as fatigue, LIP and MALT lymphoma, while inflammatory arthritis and arthralgia were frequently treated with NSAIDs, MTX or anti-TNF blockade, especially in the case of patients with overlapping phenotypes with juvenile arthritis.

Corticosteroids were frequently given in children with SS, particularly in those with systemic flares and severe disease presentations. Methylprednisolone i.v. was often prescribed as pulse therapy alongside other immunosuppressive agents to treat children with acute clinical deterioration and severe disease phenotypes, which included CNS involvement, MALT lymphoma and severe renal disease. Oral prednisolone was also used in the treatment of parotitis with good clinical response. Biologic treatments such as RTX were only reserved for children with MALT lymphoma and NMOSD, while etanercept was only given to children with various types of juvenile arthritis.

Treatment with RTX and CYC was reserved for severe cases of SS with childhood onset, with CNS involvement, MALT lymphoma, severe renal disease and PH. The clinical observations derived from this systematic review conclude that the paediatric practice aligns with the current BSR guidance for treatment of adults with SS, where RTX and CYC are reserved for patients with organ-threatening systemic complications [54].

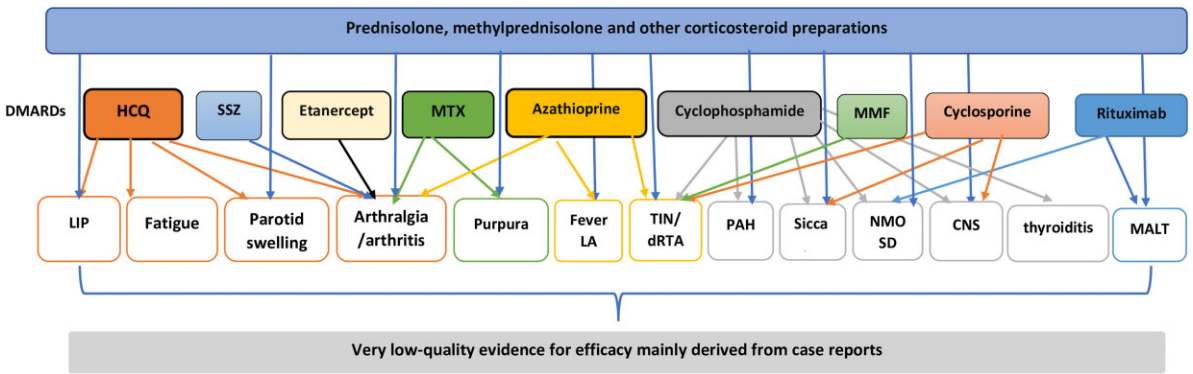
Regarding the efficacy of various treatments used in SS with childhood onset, most reports described good or stable outcomes following various expert clinician treatment choices, except for a handful of cases that described no clinical improvement or adverse effects to treatment. This may be explained by the well-recognized effect of publication bias, as clinicians reporting therapeutic success are more likely to publish their observations. Treatment with MTX, AZA, ciclosporin A and NSAIDs predominantly reported stable outcomes and improvement of symptoms overall.

It is important to note that a large proportion of treatments were given as combination therapy and therefore it is difficult to attribute the efficacy of a certain treatment Some children also had overlapping clinical phenotypes that could have driven the treatment decisions.

We summarize in Fig. 2 the main treatment choices and clinical indications for which low-quality evidence for efficacy was available. In addition, there was also an abundance of missing information from some of the case reports, including treatment dose, clinical indication for starting treatment, symptoms targeted by treatment and clinical benefit. Another limitation of case reports and case series is the lack of representability, precluding any assumption of therapeutic efficacy based on individual cases. Due to the rarity and heterogeneity in presentation of SS in children, there are currently no RCTs reported in the literature to assess the evidence for efficacy of any of the treatments available.

The poor quality of the literature data extracted by this systematic review is one of the major limitations of this report, as no reliable conclusion regarding the

FIG. 2 Treatments associated with low evidence of efficacy in SS with childhood onset and their clinical indications



LAD: lymphadenopathy.

efficacy of available therapies for SS with childhood onset can be drawn.

In conclusion, this systematic literature review demonstrates the high heterogeneity in presentation of SS in children and adolescents as well as in the use of various therapies and combinations of treatments to address their clinical manifestations.

Based on available evidence and evidence from adult disease, we can recommend the use or oral NSAIDs and corticosteroids for less severe manifestations, such as rashes, arthralgia, as first-line therapy for arthritis and for recurrent parotitis, as there is evidence of some benefit. In addition, steroid treatment was effective in treating renal disease [19, 47] or neurological manifestations [14, 38, 49] without additional DMARD therapy in some selected cases. Treatment with HCQ is recommended in patients with persistent arthralgia, myalgia and recurrent parotitis, while the use of MTX and anti-TNF blockade could be beneficial in children with persistent inflammatory arthritis. Some of the severe disease manifestations affecting kidneys, lungs and CNS are likely to benefit from pulse corticosteroid followed by gradually tapered oral therapy, in addition to stronger immunosuppressive treatments such as CYC, MMF, AZA and RTX. RTX seems to be effective in controlling psychiatric symptoms associated with SS in children and adolescents. The use of topical treatments for dryness is also recommended for symptomatic relief.

At present, there are no good-quality studies in SS with childhood onset to enable any clinical recommendations for strict selection of therapies. As the disease is rare in children compared with adults, further research into establishing validated classification criteria and disease outcome measures tailored for young people with SS is required.

In conclusion, we recommend clinicians have a higher level of suspicion for a potential diagnosis of SS in children and adolescents presenting with recurrent parotid swelling and heterogeneous clinical manifestations not explained by an alternative diagnosis at any age. Pursuing a tissue biopsy to guide the diagnosis or performing extensive SS-specific investigations is required in many cases because of the lack of validated diagnostic or classification criteria in children. Clinicians have a reasonably large therapeutic armamentarium to choose from based on patients' clinical presentation and evolution. The severe organ involvement associated with SS is likely to respond to a combination of strong immunosuppression and high steroid doses. Future research is required to establish the long-term outcomes of children with SS into adulthood. Children should also be included in adult RCTs to investigate new therapeutic strategies before good evidence-based treatment recommendations for this patient population can be made.

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Data availability statement

Data extraction files are available upon request.

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