



Clinical practice guideline for the treatment of Sjögren's disease through off-label drug use in China (English edition)

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Abstract

Objective To develop evidence-based clinical practice guideline for the treatment of primary Sjögren's disease (SJD) through off-label drug use in China, addressing the current lack of approved therapies and suboptimal management options for this autoimmune disease.

Methods The clinical questions outlined in the guideline were formulated using the PICO (Population, Intervention, Comparison, Outcome) framework, with efficacy criteria based on the STAR (Sjögren's Tool for Assessing Response) indices. Evidence retrieval encompassed databases such as PubMed, Embase, CNKI, among others up to December 31, 2022; this was supplemented by snowball searching. A multidisciplinary expert panel systematically evaluated the randomized controlled trial (RCT) evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology and formulated recommendations. Recommendations were categorized as strong (1), weak (2), or consensus-based recommendations, based on thresholds of expert agreement.

Results The guideline presents a total of 21 recommendations: including 2 strong recommendations, 14 weak recommendations, and 5 consensus-based recommendations. These encompass systemic treatments for SJD-related symptoms such as xerostomia and xerophthalmia; systemic disease activity; hypergammaglobulinemia; and considerations for special populations like pregnant patients. Key therapeutic agents include hydroxychloroquine, leflunomide, iguratimod, tripterygium glycosides, and low-dose recombinant human IL-2—employing stratified approaches according to disease severity and organ involvement. For refractory cases that do not respond adequately to initial treatments, rituximab, cyclophosphamide, and mycophenolate mofetil are recommended. The guideline emphasizes individualized treatment plans along with safety monitoring and multidisciplinary care—particularly important for high-risk groups such as pregnant women who test positive for anti-SSA antibodies.

Conclusions This guideline represents a significant advancement in the management of SJD by introducing structured approaches tailored to patient needs while highlighting areas requiring further research.

Key Points

- By disaggregating the STAR composite index into its constituent outcome measures, the guideline formulates precise clinical inquiries.
- GRADE methodology was used to provide standardized, evidence-based recommendations.
- 21 final recommendations for managing glandular, systemic, and organ-specific manifestations in SJD, considering real-world variability.
- Prioritizes domestic therapies approaches tailored for Chinese practice.

Keywords Clinical practice guideline · GRADE methodology · Off-label drug use · Sjögren's disease

Background and rationale for guideline development

Sjögren's disease (SJD) is a common systemic autoimmune disease within the field of rheumatology, with an incidence rate ranging from 6 to 12 cases per 100,000 individuals and a prevalence between 16 and 339 cases per 100,000 in China [1]. This condition affects over 4.5 million Chinese patients,

predominantly middle-aged and elderly women. SJD is characterized by dysfunction of exocrine glands, lymphocytic infiltration, and the presence of autoantibodies (e.g., anti-SSA). The clinical manifestations of SJD are diverse, encompassing glandular secretion dysfunction as well as multi-organ involvement and lymphoma.

Current treatment options for SJD remain suboptimal; there is a notable lack of evidence-based therapies addressing symptoms such as dryness, fatigue, pain, or organ damage. Consequently, management often relies on empirical approaches or adaptations derived from treatments used for rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). Despite the lack of specific indications for SJD, various systemic therapies are frequently employed in clinical practice. These include glucocorticoids (GC), hydroxychloroquine (HCQ), methotrexate (MTX), iguratimod (IGU), leflunomide, mycophenolate mofetil (MMF), cyclophosphamide (CTX), calcineurin inhibitors such as cyclosporine A (CsA) and azathioprine (AZA), rituximab (RTX), as well as plant-derived medications.

The notable deficiency in evidence-based treatment options for SJD has led the Committee for Rheumatologists and Immunologists of the Chinese Primary Health Care Foundation to assemble a multidisciplinary expert panel. Acknowledging the prevalent off-label utilization of systemic therapies, the committee sought to establish standardized pharmacotherapy practices. Employing the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology [2], we systematically evaluated randomized controlled trial (RCT) evidence concerning empirical therapies and developed the “Clinical Practice Guideline for the Treatment of Primary Sjögren's Syndrome by Off-Label Drug Use in China (2023 Edition).” The guideline was published in Chinese in the Chinese Medical Journal on November 21, 2023. This English translation aims to facilitate global dissemination of China's clinical expertise in managing SJD, thereby promoting international collaboration and comparative research while addressing the pressing need for standardized off-label treatment strategies worldwide.

Target audience

The guideline is primarily designed for healthcare professionals engaged in the diagnosis and management of SJD, including rheumatologists, ophthalmologists, stomatologists, obstetricians, and clinical pharmacists. The target patient population comprises adult individuals with confirmed SJD, explicitly excluding pediatric cases. The guideline aims to provide evidence-based recommendations to standardize pharmacological treatment, with a particular emphasis on systemic medications and off-label drug use within this demographic.

Guideline development, search methodology and dates

The development of the guideline was a collaborative endeavor undertaken by a multidisciplinary team. This team consisted of an Executive Committee, an Expert Panel, and a Grading & Development Secretariat. To uphold the integrity and objectivity of the guideline, all members formally declared no conflicts of interest pertaining to the content and recommendations presented in the guideline. This declaration is essential as it contributes to maintaining the credibility and trustworthiness of the entire guideline development process.

The search for evidence in the development of the guideline adhered to a rigorous and systematic methodology. A comprehensive retrieval of systematic evidence was conducted across an extensive array of databases, including PubMed, Embase, ClinicalTrials.gov, Cochrane Library, Web of Science, CNKI, Wanfang Data, VIP Journal, and the Chinese Biomedical Literature Database, up to December 31, 2022. In addition to this approach, snowball searching was utilized to identify pertinent studies from the references cited in related reviews, systematic reviews, meta-analyses, guidelines, and consensus statements. This thorough search strategy aimed to encompass all relevant evidence pertaining to the topic under investigation while ensuring that the guideline was grounded in the most current and comprehensive body of research available as of the specified date.

GRADE methodologies were employed to assess the quality of evidence for each recommendation, which was classified as high (A), moderate (B), or low/very low (C) in accordance with GRADE standards. For the purposes of this guideline, categories C (low) and D (very low) were combined. In instances where no evidence was available in the literature, expert consensus was categorized as C. The strength of recommendations is determined based on the following principles: (1) If the strength of agreement (SOA) for any single recommendation exceeds 50%, both the direction and level of that recommendation can be directly established; (2) If this threshold is not met but total SOA for a consistent recommendation direction surpasses 70%, then while the direction is confirmed, its level will be considered weak; (3) Should neither criterion be satisfied, further discussions will take place in subsequent stages to arrive at a final conclusion. The content includes details on wording and strength of recommendations—strong = 1; weak = 2. Moreover, if significant issues identified during the preliminary selection of clinical questions lack support from evidence-based evaluations or cannot be recommended through GRADE methodology, relevant published guidelines, consensuses, and diagnostic and treatment protocols

should be consulted. Following this process, a questionnaire will be utilized to gather experts' opinions regarding their agreement with specific recommendations. If over 70% of experts endorse a particular recommendation, it will then be recognized as a consensus-based recommendation (CR).

Key questions identified in the scope

Clinical questions were formulated utilizing the PICO (Population, Intervention, Comparison, Outcome) framework, focusing on systemic treatments for SJD identified through a comprehensive review of both domestic and international guidelines [1, 3–5], expert consultations, and analyses of package inserts. The Sjögren's Tool for Assessing Response (STAR) [6] tool was utilized to delineate composite outcomes for the formulation of clinical inquiries (Table 1). The prioritization of these questions was conducted via a Delphi survey in which experts rated the importance of each question on a 5-point scale; those receiving scores of 4 or higher were designated as key questions necessitating recommendations, while those scoring 3 or lower were excluded from further consideration. Questions that received scores between 3 and 4 were deemed important but contingent upon consensus for recommendation development.

Symptomatic treatment

Can mucolytic agents (such as N-acetylcysteine, bromhexine) promote salivary gland secretion in SJD patients?

Current treatments primarily focus on alleviating symptoms through local therapy. The 2019 European guideline advocates for stratified approaches: non-pharmacological stimulation [stimulated whole saliva flow (SWSF) > 0.7 mL/min], pharmacological stimulation (pilocarpine/anethol trithione for SWSF 0.1–0.7 mL/min), or saliva substitution (SWSF < 0.1 mL/min) [3]. It is important to note that cevimeline is not available in China, and the use of pilocarpine is limited due to adverse effects. N-acetylcysteine and bromhexine are both recommended by the 2019 European [3] and 2020 Chinese [1] guidelines for SJD in cases of residual secretion. However, neither the domestic nor international product instructions for these two medications include indications for SJD. A RCT involving 26 participants demonstrated that a four-week treatment with N-acetylcysteine significantly alleviated halitosis and daytime thirst in patients with SJD [7]. Furthermore, a case series study comprising 11 patients with SJD indicated that treatment with bromhexine (48 mg/day for 15–20 days) resulted in improvements in dry mouth symptoms among certain patients, particularly those who had experienced a shorter duration of onset [8]. Nevertheless, as these two studies focused exclusively on subjective symptoms of dry mouth without incorporating objective

Table 1 The efficacy criteria for the six questions established by disaggregating the Sjögren's Tool for Assessing Response (STAR)

No	Clinical Question	Endpoint	Efficacy Criteria
1	Which immunosuppressive drugs can promote salivary gland secretion in SJD patients?	UWSF	≥ 25% increase post-treatment vs. baseline ^{\$}
2	Which immunosuppressive drugs can stimulate lacrimal gland secretion in SJD patients?	Schirmer Test Corneal Staining Score	≥ 5 mm/5 min increase post-treatment vs. baseline* ≥ 2-point reduction post-treatment vs. baseline#
3	For SJD patients with fatigue, arthralgia, and other systemic symptoms, which immunosuppressive drugs can improve these manifestations?	ESSPRI	≥ 1-point reduction post-treatment vs. baseline or ≥ 15% improvement
4	Which immunosuppressive drugs can reduce systemic disease activity in SJD patients?	ESSDAI	≥ 3-point reduction post-treatment vs. baseline
5	Which immunosuppressive drugs can lower serum IgG levels in SJD patients?	Serum IgG concentration	≥ 10% reduction post-treatment vs. baseline
6	Which immunosuppressive drugs can decrease serum RF levels in SJD patients?	Serum RF titer	≥ 25% reduction post-treatment vs. baseline

\$: Studies that reported baseline UWSF = 0 were excluded

*: Studies that reported normal baseline Schirmer test results were excluded

#: Studies that reported normal baseline corneal staining scores were excluded

UWSF: Unstimulated Whole Saliva Flow Rate; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; RF: Rheumatoid Factor

assessment measures such as salivary flow rate, the quality of evidence remains unassessed according to GRADE methodology.

In summary, the expert panel recommends that patients with SJD experiencing mild-to-moderate salivary gland dysfunction ($\text{SWSF} \geq 0.1 \text{ mL/min}$) consider first-line systemic secretagogues such as pilocarpine or anethol trithione (the latter not being approved in China). When necessary, mucolytics like N-acetylcysteine—administered at a dosage of 0.2 g two to three times daily or as effervescent tablets of 600 mg two to three times daily—or bromhexine at doses ranging from 8–16 mg three times daily can be considered as alternative options, with monitoring for potential hiccups.

Recommendation

For SJD patients with residual salivary gland function (mild-to-moderate impairment of glandular secretory) who are intolerant or unreachable to muscarinic drugs, N-acetylcysteine and bromhexine can be considered to promote salivary gland secretion (CR, C) (SOA 92%).

Systemic management

Which systemic immunosuppressive drugs can promote salivary gland secretion in SJD patients?

It has been reported that the combination therapy of HCQ and leflunomide demonstrated a significant improvement in unstimulated whole saliva flow (UWSF), with a mean difference (MD) of 0.011 mL/min and a 95% confidence interval (CI) of 0.002 to 0.019, based on data from 29 participants. This result exceeded the established threshold for a $\geq 25\%$ response as defined by the STAR criteria [9]. In contrast, the tripterygium-total glucosides of paeony (TGP) regimen exhibited superior efficacy compared to monotherapy of tripterygium (MD=0.05 mL/min, 95% CI: 0.04~0.06, $n=98$) [10].

Conversely, while tripterygium glycosides alone achieved an increase in UWSF $\geq 25\%$, it lacked placebo controls [11]. Furthermore, HCQ monotherapy did not produce statistically significant improvements in UWSF (MD=0.03 mL/min, 95% CI: -0.03~0.12, $n=75$) [12]. Other agents—including IGU, RTX, and TGP administered alone—demonstrated inconsistent or subthreshold effects ($< 25\%$ increase in UWSF), supported by limited evidence [13–18].

In summary, the expert panel recommends that for SJD patients who are experiencing obvious salivary hypofunction (baseline UWSF $\leq 0.1 \text{ mL/min}$), two evidence-based immunosuppressive regimens can be prioritized according

to the strength of expert consensus: (1) HCQ at a dosage of 5 mg/(kg·d) combined with leflunomide at a dose of 10–20 mg/d, which has garnered the strongest support; and (2) Tripterygium glycosides in conjunction with TGP at a dosage range of 1,200–1,800 mg/d. The timing of treatment aimed at enhancing salivary gland secretion in SJD patients who are undergoing systemic immunosuppressive therapy should be stratified based on the functional status of the salivary glands. However, there is currently a significant lack of relevant research addressing this issue. Some experts have underscored that when formulating immunosuppressive drug regimens for SJD patients to mitigate reduced salivary gland secretion, it is crucial to concurrently consider both the overall disease activity as indicated by the European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index (ESSDAI) and biomarker levels, such as serum IgG.

Recommendation

For SJD patients with decreased salivary gland secretion: a. HCQ plus leflunomide may increase the rate of UWSF (2, C) (SOA 84%); b. Tripterygium glycosides plus TGP may increase the rate of UWSF (2, C) (SOA 73%).

Which systemic immunosuppressive drugs can promote lacrimal gland secretion in SJD patients?

It has been reported that the combination of HCQ and TGP significantly improved lacrimal gland function (MD=2.69 mm/5 min, 95% CI: 1.03~4.36, $I^2=88\%$, $n=183$), achieving STAR response criteria ($\geq 5 \text{ mm/5 min}$ increase) [19–21]. In contrast, MTX plus TGP showed no significant benefit (MD=0.49 mm/5 min, 95% CI: -0.21~1.15, $I^2=83\%$, $n=134$) [20, 21], while other regimens (HCQ plus leflunomide, tripterygium glycosides, IGU, RTX, TGP alone, methylprednisolone combinations, CsA) either failed to reach the 5 mm/5 min threshold or demonstrated inconsistent effects [9, 10, 13–15, 17, 22–26]. Notably, HCQ monotherapy showed variable efficacy (inconsistent reporting across studies) and failed to meet STAR criteria in a dedicated RCT (Δ corneal staining < 2 points) [27].

In summary, the expert panel strongly recommends that for refractory SJD patients experiencing severe dry eye syndrome—defined as a Schirmer's test result of $\leq 5 \text{ mm/5 min}$ in at least one eye—that is unresponsive to topical therapies, a combination of HCQ at 5 mg/(kg·d) and TGP at 1,200–1,800 mg/d can be considered. This recommendation is supported by a 52% consensus among experts for its strong endorsement. The experts emphasize the necessity for future clinical trials to adopt

STAR criteria that integrate both Schirmer's test results and corneal staining scores to ensure a comprehensive assessment of efficacy.

Recommendation

For SJD patients with reduced lacrimal gland secretion, HCQ plus TGP is recommended to improve ocular Schirmer's test (1, B) (SOA 97%).

Systemic symptoms such as dryness, fatigue, and limb pain are common complaints or primary reasons for seeking medical attention in SJD patients. Which immunosuppressive drugs can improve these systemic symptoms?

It has been reported that TGP alone significantly improved EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) (MD = -0.52 , 95% CI: $-0.93 \sim -0.11$, $I^2 = 83\%$, $n = 326$), indicating a reduction of $\geq 15\%$ from baseline [18, 22]. In contrast, low-dose GC combined with IGU demonstrated superior efficacy compared to GC plus HCQ (MD = -2.08 , 95% CI: $-2.45 \sim -1.71$, $I^2 = 0$, $n = 180$), achieving at least a one-point reduction in ESSPRI [23, 24]. Ineffective alternatives include the combination of HCQ and leflunomide (showing no significant difference versus placebo) [9], IGU monotherapy (which provided no statistical benefit) [13], HCQ monotherapy (< 1 -point reduction in ESSPRI) [12], and RTX (< 1 -point reduction in ESSPRI) [16]. In summary, the expert panel recommends that for SJD patients who are experiencing core symptoms such as dryness, fatigue, and pain, either TGP at a dosage of 1,200–1,800 mg per day or low-dose GC (prednisone-equivalent 10 mg per day) in conjunction with IGU at a dose of 25 mg twice daily is advised.

Recommendation

For SJD patients with symptoms such as dryness, fatigue and pain: a. It is recommended to use TGP alone to decrease ESSPRI (1, A) (SOA 96%); b. Low-dose GC plus IGU may decrease ESSPRI (2, B) (SOA 73%).

Which immunosuppressive drugs can improve the systemic disease activity in SJD patients?

Two treatment regimens significantly improved ESSDAI, achieving a reduction of at least 3 points as per STAR criteria [9, 23–25]. The combination of HCQ and leflunomide demonstrated greater efficacy (MD = -4.35 , 95% CI: $-7.45 \sim -1.25$, $n = 29$), while the low-dose GC combined with IGU also showed notable effectiveness (MD = -1.90 ,

95% CI: $-2.56 \sim -1.25$, $I^2 = 0$, $n = 300$). In contrast, ineffective alternatives included HCQ monotherapy, IGU monotherapy, TGP monotherapy, and tripterygium glycosides monotherapy—all resulting in less than a 3-point reduction in ESSDAI scores [12, 13, 22, 28]. RTX exhibited inconsistent responses in ESSDAI across various studies [14, 16, 29], and immunosuppressants such as CTX/MTX lack direct data on ESSDAI endpoints.

In summary, the expert panel recommends that for SJD patients exhibiting moderate to severe disease activity (ESSDAI ≥ 5), two evidence-based treatment regimens are advised to mitigate systemic inflammation: (1) HCQ at a dosage of 5 mg/(kg·d) in conjunction with leflunomide at 10–20 mg/d, which is supported by a stronger evidence base; and (2) low-dose GC, specifically prednisone-equivalent at 10 mg/d, combined with IGU administered as 25 mg twice daily. Additionally, short-term intensive GC therapy is considered for cases presenting organ-threatening disease.

Recommendation

For SJD patients with moderate and severe systemic disease activity: a. Low-dose GC plus IGU may decrease ESSDAI (2, B) (SOA 86%); b. HCQ plus leflunomide may decrease ESSDAI (2, C) (SOA 89%).

Which immunosuppressive drugs can reduce serum IgG in SJD patients?

Five treatment regimens demonstrated a reduction of $\geq 10\%$ in IgG levels from baseline, according to the STAR criteria: (1) HCQ combined with TGP exhibited the most pronounced effect (MD = -3.23 g/L, 95% CI: $-5.18 \sim -1.28$, $I^2 = 36\%$, $n = 187$) [19–21]; (2) Tripterygium glycosides alone showed significant efficacy (MD = -3.70 g/L, 95% CI: $-4.61 \sim -2.79$, $I^2 = 60\%$, $n = 310$) [28, 30–33]; (3) Low-dose GCs combined with IGU also proved superior to GCs plus HCQ (MD = -2.38 g/L, 95% CI: $-3.13 \sim -1.63$, $I^2 = 0\%$, $n = 478$) [23, 24, 34–37]; (4) IGU monotherapy significantly reduced IgG levels (MD = -8.50 g/L, 95% CI: $-12.75 \sim -4.25$, $n = 55$) [16]; and (5) HCQ combined with leflunomide (MD = -3.32 g/L, 95% CI: $-5.28 \sim -1.37$, $n = 29$) [9]. However, there is insufficient evidence supporting the use of TGP alone or either HCQ or RTX as standalone treatments [12, 14, 17–22, 29, 31, 32].

In summary, the expert panel recommends that for SJD patients exhibiting elevated serum IgG levels, five evidence-based treatment regimens can be considered to reduce IgG concentrations, ranked according to the strength of expert consensus: (1) HCQ at a dosage of 5 mg/(kg·d) combined with TGP at 1,200–1,800 mg/d; (2) Tripterygium glycosides alone at a dosage of 1 mg/kg/d or 20 mg three times daily; (3) Low-dose GC, equivalent to

prednisone at 10 mg/d, in conjunction with IGU at 25 mg twice daily; (4) IGU administered as monotherapy; and (5) HCQ combined with leflunomide at a dose of 20 mg/d. For patients presenting isolated elevations in IgG without organ involvement, low-toxicity regimens should be prioritized. Cases characterized by significant IgG elevation that are refractory to conventional therapies necessitate hematologic evaluation to rule out alternative causes of hypergammaglobulinemia.

Recommendation

For SJD patients with elevated serum IgG: a. HCQ plus TGP can be considered to reduce serum IgG (2, B) (SOA 96%); b. Low-dose GC plus IGU can be considered to reduce serum IgG (2, B) (SOA 80%); c. Tripterygium glycosides can be considered to reduce serum IgG (2, B) (SOA 77%); d. IGU can be considered to reduce serum IgG (2, C) (SOA 89%); e. HCQ plus leflunomide can be considered to reduce serum IgG (2, C) (SOA 81%).

Which immunosuppressive drugs can reduce serum rheumatoid factor (RF) in SJD patients?

For SJD patients exhibiting elevated serum RF—a recognized independent predictor of lymphoma [6, 38] and a critical component of the Composite Response Index for SJD (CRESS) [39]—three treatment regimens achieved a reduction in RF levels of $\geq 25\%$ from baseline, meeting the STAR criterion. Notably, the combination of GC and IGU demonstrated significant superiority over GC combined with HCQ (MD = -5.43 U/ml, 95% CI: $-8.45 \sim -2.41$; $I^2 = 78\%$; $n = 478$) [23, 24, 34–37]. Additionally, MTX combined with TGP outperformed MTX monotherapy (MD = -10.50 U/ml, 95% CI: $-15.43 \sim -5.57$; $n = 56$) [20]. Furthermore, tripterygium glycosides administered as monotherapy also exhibited efficacy compared to HCQ (MD = -22.80 U/ml, 95% CI: $-39.37 \sim -6.23$, $n = 59$) [31]. Conversely, less robust options such as RTX and HCQ monotherapy were deemed less supported due to inconsistent evidence [14, 15, 20, 23].

In summary, the expert panel recommends that three treatment regimens can be considered: (1) low-dose GC (prednisone-equivalent 10 mg/d) plus IGU 25 mg bid; (2) MTX 10 mg/week plus TGP 1,200–1,800 mg/d; and (3) tripterygium glycosides 1 mg/kg/d alone. For patients with isolated RF elevation and no organ involvement, treatment decisions should balance benefits against potential adverse effects, favoring low-toxicity regimens. Cases with persistent RF elevation despite conventional therapy require lymphoma exclusion.

Recommendation

For SJD patients with elevated serum RF: a. Low-dose GC plus IGU can be considered to reduce serum RF (2, B) (SOA 73%); b. MTX plus TGP can be considered to reduce serum RF (2, C) (SOA 69%); c. Tripterygium glycosides can be considered to reduce serum RF (2, C) (SOA 66%). Notably, for patients who present with isolated elevations in RF and exhibit no signs of organ involvement, treatment should prioritize low-toxicity regimens.

Extras and special issues

Which immunosuppressive drugs can improve inflammatory musculoskeletal pain in SJD patients?

Evidence from a case–control study [40] demonstrated the efficacy of HCQ in improving joint tenderness and swelling (MD = -7.0 , 95% CI: $-8.3 \sim -5.7$, $n = 35$), as well as in reducing GC dosage (MD = -5.00 mg/d, 95% CI: $-6.76 \sim -3.24$, $n = 35$). MTX exhibited similar GC-sparing effects (MD = -4.00 mg/d, 95% CI: $-8.61 \sim 0$, $n = 17$). A prospective trial [41] further confirmed the benefits of CsA in decreasing tender joint counts (MD = -5.80 , 95% CI: $-10.02 \sim -1.58$, $n = 30$) and swollen joint counts (MD = -1.90 , 95% CI: $-2.99 \sim -0.81$, $n = 30$).

These findings are consistent with the 2017 Sjögren's Syndrome Foundation guideline [4], which recommend HCQ as the first-line therapy due to its anti-inflammatory properties and favorable safety profile; MTX is suggested as a second-line option for cases resistant to HCQ treatment. Additionally, the 2020 Chinese SJD Specification [1] recommends MTX or leflunomide for arthritis management.

In summary, the expert panel recommends that for SJD patients experiencing joint symptoms, HCQ at a dosage of 5 mg/(kg·d) or CsA at 1–3 mg/(kg·d) can be considered for alleviating joint pain and swelling. Additionally, HCQ or MTX at a dose of 10 mg per week may be considered to reduce GC dependence in cases of inflammatory musculoskeletal pain. The expert panel endorsed these treatment strategies with a consensus of 92%, highlighting the importance of GC-sparing approaches while acknowledging the limited evidence from RCT for certain agents.

Recommendation

SJD patients with inflammatory musculoskeletal pain can consider using HCQ and CsA to reduce joint swelling and tenderness; and using HCQ and MTX to reduce the dosage of GC (CR, C) (SOA 92%).

Which immunosuppressive drugs are effective in treating interstitial lung disease (ILD) caused by SJD?

Evidence from retrospective studies supports the survival benefit of CTX (MD=43.72 months, 95% CI: 24.24~63.20, $n=113$) [42], as well as the improvements in pulmonary function associated with MMF, specifically an increase in the percentage of diffusing capacity of the lung for carbon monoxide (DLCO%, MD=2.5%, 95%CI: 0~6.1%, $n=7$) and an increase in the percentage of forced vital capacity (FVC%, MD=11.9%, 95%CI: 1.5%~22.3%, $n=7$) [43]. In contrast, RTX and CsA demonstrated no significant efficacy [43–48]. Recommendations are consistent with international guidelines [1, 3, 5]: (1) GC at a dosage of 0.5 mg/kg/day should be considered first-line treatment for moderate ESSDAI, particularly in cases involving lymphocytic or organizing ILD; (2) Oral immunosuppressants such as MMF or AZA, preferably MMF, are recommended for long-term management; (3) CTX or RTX is indicated for cryoglobulinemic vasculitis. The 2021 International Consensus [5] advocates for GC induction followed by maintenance therapy with MMF/AZA for symptomatic ILD.

In summary, the expert panel recommends that for SJD patients who have ILD, immunosuppressive therapy can be initiated only after active infections have been excluded. Based on infection control considerations, CTX at a dosage of 50–150 mg orally per day or 0.5–1.0 g/m² intravenously every four weeks, or MMF at a dosage of 1.5–2.0 g per day are considered, accompanied by close monitoring of blood counts, liver and kidney function, as well as infection prevention measures (e.g., *Pneumocystis* prophylaxis). It is important to note that CTX poses reproductive toxicity risks for patients with fertility concerns. Due to the limited evidence from RCTs, optimal dosing regimens, treatment duration, and criteria for discontinuation of CTX/MMF remain undetermined. This recommendation is classified as weak; however, it reflects a high level of expert consensus at 96%, underscoring the necessity for ILD subclassification-guided therapy while emphasizing the need for further research into antifibrotic agents and classification-specific protocols.

Recommendation

SJD patients with ILD can consider using CTX and MMF, in which CTX can prolong the survival time of patients, and MMF can improve pulmonary diffusion function (CR, C) (SOA 96%).

Which immunosuppressive drugs are effective in treating thrombocytopenia caused by SJD?

Evidence from case series indicates that tacrolimus achieves a complete platelet response ($\geq 100 \times 10^9/L$ without bleeding) in 61% of patients after 24 weeks [49]. In contrast, CsA at a dosage of 100 mg/day combined with prednisone improves platelet counts in 87% of cases [50]. Retrospective studies reveal that RTX yields higher platelet response rates (81%) compared to CsA (odds ratio[OR]=4.89, 95% CI: 1.64~14.58, $n=83$) [51, 52]. Current guidelines recommend a treatment sequence beginning with first-line GC, specifically prednisone-equivalent doses ranging from 0.5 to 1.0 mg/kg/day for thrombocytopenia presenting as $< 20 \times 10^9/L$, escalating to GC plus intravenous immunoglobulin (IVIg) or RTX for non-responders [1, 3]. Salvage options may include plasma exchange or CTX. Despite the clinical application of IVIg, no supporting evidence has been identified.

In summary, the expert panel recommends that for SJD patients who experience refractory thrombocytopenia despite GC therapy, the following treatment options can be considered: tacrolimus (2–3 mg/day with therapeutic drug monitoring), CsA (2–3 mg/kg/day), or RTX (200–500 mg administered every 1–2 weeks for a total of 1–3 doses). It is important to note that RTX requires pre-treatment screening for hepatitis B; specifically, positivity for HBsAg or anti-HBcAb necessitates prophylactic antiviral therapy. The expert panel endorsed these recommendations with a consensus of 96%, highlighting the importance of infection screening—particularly for hepatitis B—and advocating for individualized ILD subclassification prior to RTX administration.

Recommendation

SJD patients with refractory thrombocytopenia can consider using tacrolimus, CsA or RTX to increase platelets levels and help reduce GC (CR, C) (SOA 96%).

The domestic instruction manual for recombinant human IL-2 indicates SJD as an indication. Should the subcutaneous injection dosage for SJD follow the manual?

Currently, there are two types of recombinant human IL-2 approved for SJD indication with subcutaneous injection instructions in China: (1) Recombinant Human IL-2 for Injection: 200,000 to 1,000,000 U per administration, administered 1 to 2 times daily over a course of 15–20 days; (2) Recombinant Human IL-2 (125A1a): 600,000 to 1,000,000 U/m², administered via subcutaneous injection three times per week over a duration of six weeks. Evidence from a

pivotal RCT [53] demonstrated a significant reduction in the ESSDAI with low-dose recombinant human IL-2 compared to placebo (MD = −3.67, 95% CI: −4.58 ~ −2.76, $n=60$), achieving at least a three-point improvement in systemic disease activity. This dosing strategy was optimized based on the bidirectional immune regulatory properties of

IL-2—lower doses selectively expand regulatory T cells while mitigating the excessive pro-inflammatory effects associated with higher doses used for other autoimmune conditions such as graft-versus-host disease, vasculitis, and SLE [54–56].

Table 2 Recommendations for the guideline

Recommendations for the guideline		Quality of Recommendations Δ /Evidences Δ	SOA
1 Symptomatics treatment			
1.1	For SJD patients with residual salivary gland function (mild-to-moderate impairment of glandular secretory) who are intolerant or unreachable to muscarinic drugs, N-acetylcysteine and bromhexine can be considered to promote salivary gland secretion	CR, C	92%
2 Systemic management			
2.1	For SJD patients with decreased salivary gland secretion:		
	a. HCQ plus leflunomide may increase the rate of UWSF	2, C	84%
	b. Tripterygium glycosides plus TGP may increase the rate of UWSF	2, C	73%
2.2	For SJD patients with reduced lacrimal gland secretion, HCQ plus TGP is recommended to improve ocular Schirmer's test	1, B	97%
2.3	For SJD patients with symptoms such as dryness, fatigue and pain:		
	a. It is recommended to use TGP alone to decrease ESSPRI	1, A	96%
	b. Low-dose GC plus IGU may decrease ESSPRI	2, B	73%
2.4	For SJD patients with moderate and severe systemic disease activity:		
	a. Low-dose GC plus IGU may decrease ESSDAI	2, B	86%
	b. HCQ plus leflunomide may decrease ESSDAI	2, C	89%
2.5	For SJD patients with elevated serum IgG:		
	a. HCQ plus TGP can be considered to reduce serum IgG	2, B	96%
	b. Low-dose GC plus IGU can be considered to reduce serum IgG	2, B	80%
	c. Tripterygium glycosides can be considered to reduce serum IgG	2, B	77%
	d. IGU can be considered to reduce serum IgG	2, C	89%
	e. HCQ plus leflunomide can be considered to reduce serum IgG	2, C	81%
2.6	For SJD patients with elevated serum RF*:		
	a. Low-dose GC plus IGU can be considered to reduce serum RF	2, B	73%
	b. MTX plus TGP can be considered to reduce serum RF	2, C	69%
	c. Tripterygium glycosides can be considered to reduce serum RF	2, C	66%
3 Extras and special issues			
3.1	SJD patients with inflammatory musculoskeletal pain can consider using HCQ and CsA to reduce joint swelling and tenderness; and using HCQ and MTX to reduce the dosage of GC	CR, C	92%
3.2	SJD patients with ILD can consider using CTX and MMF, in which CTX can prolong the survival time of patients, and MMF can improve pulmonary diffusion function	CR, C	96%
3.3	SJD patients with refractory thrombocytopenia can consider using tacrolimus, CsA or RTX to increase platelets levels and help reduce GC	CR, C	96%
3.4	SJD patients exhibiting moderate and severe systemic disease activity can receive treatment with recombinant human IL-2. The prescribed dosage, lower than the recommended dosage in the product instructions, is 500,000 ~ 1,000,000 U/m ² per administration, given subcutaneously every other day for a duration of 2 weeks, with a cessation of drug intake for 2 weeks. This process constitutes a course of treatment for 3 consecutive courses, totaling 12 weeks	2, B	73%
3.5	For pregnant SJD patients with positive anti-SSA, if there is no contraindication or intolerance, HCQ can be used during pregnancy to prevent the occurrence of CHB	CR, C	96%

*Notably, for patients who present with isolated elevations in RF and exhibit no signs of organ involvement, treatment should prioritize low-toxicity regimens. Δ 1: strong, 2: weak, CR: consensus-based recommendations. Δ A: high, B: moderate, C: low/very low

SOA strength of agreement

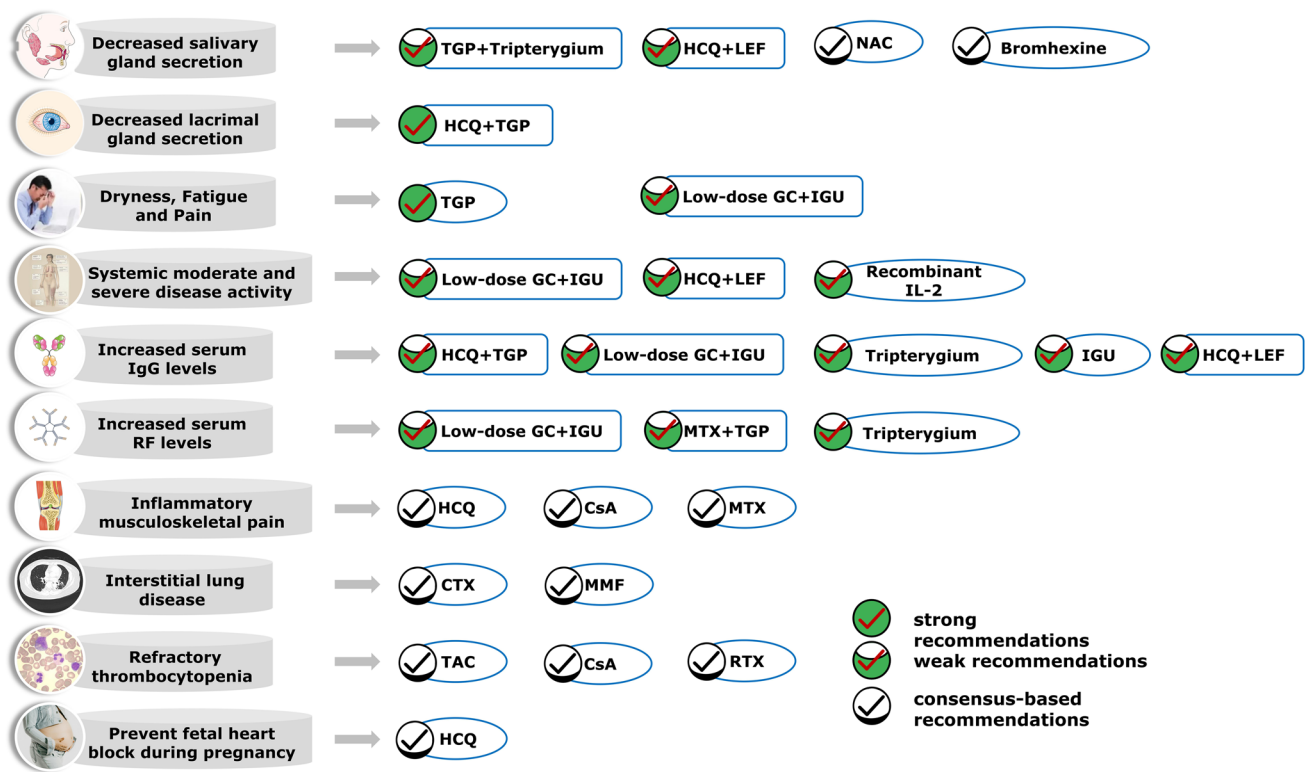


Fig. 1 Recommendations for the guideline. TGP: total glucosides of paeony, HCQ: hydroxychloroquine, LEF: leflunomide, NAC: N-acetylcysteine, GC: glucocorticoid, IGU: iguratimod, CsA: cyclosporine

A, MTX: methotrexate, CTX, cyclophosphamide, MMF: mycophenolate mofetil, TAC: tacrolimus, RTX: rituximab

In summary, the expert panel recommends that for SJD patients exhibiting moderate to severe disease activity ($\text{ESSDAI} \geq 5$), low-dose recombinant human interleukin-2 is advised as an immunomodulatory therapy. The proposed regimen consists of administering 500,000–1,000,000 U/m² subcutaneously every other day for a duration of two weeks (a 2-week course), followed by a subsequent 2-week drug holiday, culminating in three consecutive courses over a total period of 12 weeks. This treatment protocol effectively balances efficacy and safety, with transient injection-site reactions—including redness, induration, and pain—as well as constitutional symptoms such as fever and chills that typically resolve spontaneously. The expert panel endorsed this approach with a total recommendation vote of 73% (27% strong support and 46% weak support), reflecting its favorable risk–benefit profile for the management of SJD.

Recommendation

SJD patients exhibiting moderate and severe systemic disease activity can receive treatment with recombinant human IL-2. The prescribed dosage, lower than the recommended dosage in the product instructions, is 500,000~1,000,000 U/m² per administration, given subcutaneously every other day

for a duration of 2 weeks, with a cessation of drug intake for 2 weeks. This process constitutes a course of treatment for 3 consecutive courses, totaling 12 weeks (2, B) (SOA 73%).

The domestic instruction manual for HCQ states that it should be used with caution in pregnant women. Can HCQ be used to prevent congenital heart block (CHB) in pregnant SJD patients with positive anti-SSA?

Pregnant SJD patients face significantly elevated risks of maternal complications such as respiratory distress syndrome, disseminated intravascular coagulation, pulmonary edema, and preeclampsia [57, 58]. Additionally, adverse fetal outcomes may occur, including fetal distress, low birth weight, prematurity, and CHB [58, 59]. The package insert of domestic HCQ products includes warnings regarding potential teratogenic effects—such as ototoxicity and retinal damage—and the FDA classifies HCQ as category C during pregnancy.

The "2022 Chinese Guideline for Reproductive and Pregnancy Management of Patients with Systemic Lupus Erythematosus" advises that pregnant SLE patients who are positive for anti-SSA should undergo fetal echocardiography

every two weeks starting from 16 weeks of gestation until reaching 26–28 weeks of gestation [60]. In contrast, the American College of Maternal–Fetal Medicine Consultation Series does not endorse routine use of fetal echocardiography specifically to assess the time interval from P-wave to R-wave (PR interval) [61]. A case–control study, along with two cohort studies, assessed the efficacy of HCQ in mitigating the risk of CHB during pregnancy among patients with SLE ($n = 261$) and SJD ($n = 74$) who tested positive for anti-SSA antibodies [62–64]. The findings indicated that HCQ could significantly lower the risk of neonatal lupus-associated cardiac disease in the fetus ($OR = 0.25$, $95\%CI: 0.13 \sim 0.49$, $n = 498$, $I^2 = 0$).

In summary, the expert panel recommends that for anti-SSA-positive SJD patients, the administration of HCQ at a dosage of 5 mg/(kg·d) throughout pregnancy to mitigate the risk of CHB.

Recommendation

For pregnant SJD patients with positive anti-SSA, if there is no contraindication or intolerance, HCQ can be used during pregnancy to prevent the occurrence of CHB (CR, C) (SOA 96%).

Applicability and utility

This guideline distinguishes itself from existing domestic and international SJD management recommendations by employing the GRADE methodology, which ensures standardization, rationality, and transparency in evidence grading and recommendation formulation. Unlike conventional approaches, this guideline not only requires statistically significant superiority over control groups in RCTs but also mandates adherence to the STAR response criteria for efficacy evaluation. By decomposing the STAR composite index into individual outcome measures (e.g., ESSDAI, ESSPRI, Schirmer's test, UWSF, IgG, and RF), the guideline designs precise clinical questions, conducts systematic evidence retrieval, meta-analysis, and GRADE-based quality assessment following the PICO principle. This rigorous methodology enhances the clinical applicability of the recommendations, ensuring that the 21 final recommendations (Table 2)—including 2 strong, 14 weak, and 5 consensus-based—are grounded in robust evidence while accommodating real-world clinical variability. The recommendations are depicted in Fig. 1, demonstrating their broad applicability by addressing a wide range of symptoms, systemic and organ-specific issues, as well as special populations. They provide significant utility through evidence-based, consensus-driven, and practical treatment guidance aimed at optimizing patient care.

Research recommendations

A key strength of this guideline is its focus on domestically developed and widely used therapies, such as IGU and plant-derived agents (e.g., tripterygium glycosides, TGP), which are more relevant to Chinese clinical practice than internationally approved drugs. However, the guideline acknowledges emerging therapies (e.g., B-cell-targeted biologics like telitacicept and JAK inhibitors) that may benefit refractory SJD patients with organ involvement, though their efficacy remains under investigation and thus warrants exclusion from current recommendations. The evidence review process also highlights critical unresolved clinical questions, including the management of SJD-related peripheral neuropathy, central nervous system involvement, renal tubular acidosis, and ILD. Future research should prioritize high-quality RCTs to address these gaps, particularly for off-label drug use, biologics, and targeted therapies, to provide stronger evidence for future guideline updates.

Conclusions

This guideline represents a significant advancement in SJD treatment by integrating GRADE methodology with STAR/CRESS response criteria, ensuring evidence-based yet flexible recommendations for off-label drug use. Its inclusion of domestically developed therapies (e.g., IGU, TGP) enhances relevance to Chinese patients, while its consensus-based recommendations fill evidence gaps where RCTs are lacking. However, the guideline emphasizes that its recommendations are not legally binding but serve as a clinical reference to standardize off-label prescribing. Clinicians must individualize treatment based on patient conditions, drug accessibility, and reimbursement policies while monitoring for adverse events. The guideline's identification of urgent unmet needs (e.g., ILD, fetal cardiac monitoring in pregnancies with positive anti-SSA) underscores the necessity for future high-quality trials to refine SJD management strategies and improve patient outcomes.

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Data availability All data that support the findings of this study are included in this manuscript and its supplementary information files.

Declarations

Ethical standards The manuscript does not contain clinical studies or patient data.

Conflict of interest The authors report there are no competing interests to declare.

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