Mechanism-driven innovative drug development for Sjögren's disease: insights from global clinical trial landscapes

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Sjögren's disease (SjD) is a systemic autoimmune disorder characterised by leading to progressive glandular dysfunction, systemic inflammation, and diminished quality of life (1-3). Conventional therapies, including hydroxychloroquine (HCQ), corticosteroids, and immunosuppressants, provide limited symptom relief and are often limited by adverse effects (4, 5). These limitations highlight the critical need for therapies targeting SjD pathogenesis rather than symptomatic manifestations. Recent advances have identified key therapeutic targets, including the JAK-STAT pathway, CD40-CD40L axis, and M3 muscarinic acetylcholine receptor (M3R) agonism (6). Moreover, breakthroughs in biologic engineering such as bispecific antibodies and CAR-T cell therapy have expanded the therapeutic toolkit (7). Together, these developments have catalysed a surge in mechanism-driven clinical trials aiming to redefine SjD management. Here, we analyse global trends in SjD clinical trials, with a focus on mechanism-driven drug development. Our study maps the evolving therapeutic landscape, prioritising strategies that address both glandular dysfunction and systemic autoimmunity.

This study analysed a total of 228 worldwide clinical trials (1997-2025) extracted from the Trialtrove database (https://clinicalintelligence.citeline.com/) to map the therapeutic landscape of SjD. This analysis focused exclusively on interventional clinical trials. Non-interventional studies, purely observational studies, and pharmacokinetic trials were excluded to ensure the analysis was concentrated on trials with defined therapeutic interventions and efficacy endpoints. We utilised the retrieval strategy: "Disease is Autoimmune/Inflammation: Sjögren's Syndrome". Trials containing patients with concomitant autoimmune diseases or secondary SS were excluded. Variables analysed included: 1) Trial design (phase, status, sponsor, country); 2) Intervention profile (drug, mechanism, target); 3) Outcomes. Through this approach, we highlight emerging opportunities to redefine SjD management through mechanism-driven innovation.

A marked increase of SjD clinical trials accelerating translational momentum, with Phase II studies dominating therapeutic development. Our analysis of trials revealed a 9.05% compound annual growth rate, especially since 2020 with continuous registrations exceeding 10 cases (Fig. 1A). Phase-specific stratification showed Phase II trials constituting nearly half of all investigations (49.35%, n=113), while Phase I activity surged in 2024-2025 (n=14), signalling intensified novel target exploration. Notably, 47 Phase IV trials focused on clarifying controversies surrounding legacy agents like HCQ (n=8) and belimumab (n=6), reflecting persistent uncertainties in standard care (Fig. 1B, Table I).

Our analysis delineated distinct therapeutic priorities in SjD trials: salivary gland involvement predominated (78 trials, 34.2%), followed by ocular manifestations (56 trials, 24.6%), while visceral and systemic domains remained underrepresented (Fig. 1C). HCQ emerged as the primary glandular agent (oral:15 trials; ocular:8 trials), though natural products surpassed it in ocular symptom trials (n=10 *vs*. HCQ's 8). Systemic therapies remained nascent, limited to exploratory approaches like QH-103 (T-cell stimulator, n=3) and CD19 CAR-T (n=2). This gland-centric bias highlights unmet needs in managing SjD multisystemic nature (Fig. 1D).

Target engagement analysis delineated three strategic axes driving mechanism-driven innovation. Therapeutic targets clustered around: 1) B-cell depletion via CD20 (MS4A1, n=32) and CD19 (n=15); 2) Secretory restoration through M3R agonism (n=12); and (3) Cytokine modulation targeting BAFF receptor (TNFRSF13B, n=11) and JAK1 (n=10) (Fig. 1E). The therapeutic landscape remains dominated by conventional immunosuppressants (HCQ, n=16) and B-cell-targeted biologics (rituximab/belimumab cohort, n=15). Notably, pathway-selective agents such as JAK-STAT inhibitors (n=5) and BAFF/APRIL modulators (n=5), show emerging traction, signalling an evolving treatment paradigm (Fig. 1F). This targeting framework bridges immediate clinical needs with long-term curative ambitions.

Translational success hinges on geographic and sectoral collaboration, with academia currently driving innovation. As illustrated in Figure 1G, geographic analysis showed U.S. leadership (36%, n=83) and China's rising prominence (24%, n=55), collectively hosting 60% of global trials. Academic institutions spearheaded 60.05% of trials (n=137) *versus* 30% industry-sponsored trials (n=68), with minimal Top 20 Pharma engagement (n=7) (Fig. 1H). Approximate-

Table I. Clinical outcomes of hydroxychloroquine trails.

TrialTroveID	Patient segment	Primary tested drug	Trial outcomes
519086	Ocular symptoms; oral symptoms; Primary Sjögren's syndrome	hydroxychloroquine sulphate Acupuncture	Completed, Outcome unknown
417870	Primary Sjögren's syndrome	leflunomide hydroxychloroquine sulphate mycophenolate mofetil, unspecified	Completed, positive outcome/primary endpoint(s) met
412715	Primary Sjögren's syndrome	hydroxychloroquine sulphate natural product	Completed, outcome unknown
412040	Primary Sjögren's syndrome	hydroxychloroquine sulphate baricitinib	Completed, negative outcome/primary endpoint(s) not met
397429	Primary Sjögren's syndrome	leflunomide hydroxychloroquine sulphate	Completed, outcome unknown
384506	Comorbidities in dry eye syndrome; mild to moderate; moderate to severe; ocular symptoms; primary Sjögren's syndrome;	hydroxychloroquine sulphate	Completed, outcome unknown
343856	Oral symptoms; primary Sjögren's syndrome	hydroxychloroquine sulphate iguratimod, unspecified	Completed, Outcome unknown
317392	Primary Sjögren's syndrome	hydroxychloroquine sulphate mesenchymal stem cells, unspecified	Terminated, planned but never initiated; Terminated, Unknown
155063	Non-sicca symptoms; Oral symptoms; primary Sjögren's syndrome	hydroxychloroquine sulphate natural product	Completed, negative outcome/primary endpoint(s) not met

This table summarises clinical outcomes of trials investigating hydroxychloroquine sulphate in patients with SjD or related symptom subsets. (TrialTroveID: unique identifier for each trial in the Trialtrove database; patient segment: clinical population enrolled (*e.g.* primary SjD with ocular/oral symptoms, comorbid dry eye syndrome); primary tested drug: hydroxychloroquine sulphate and comparator interventions; trial outcomes: completion status and whether primary efficacy endpoints were met).

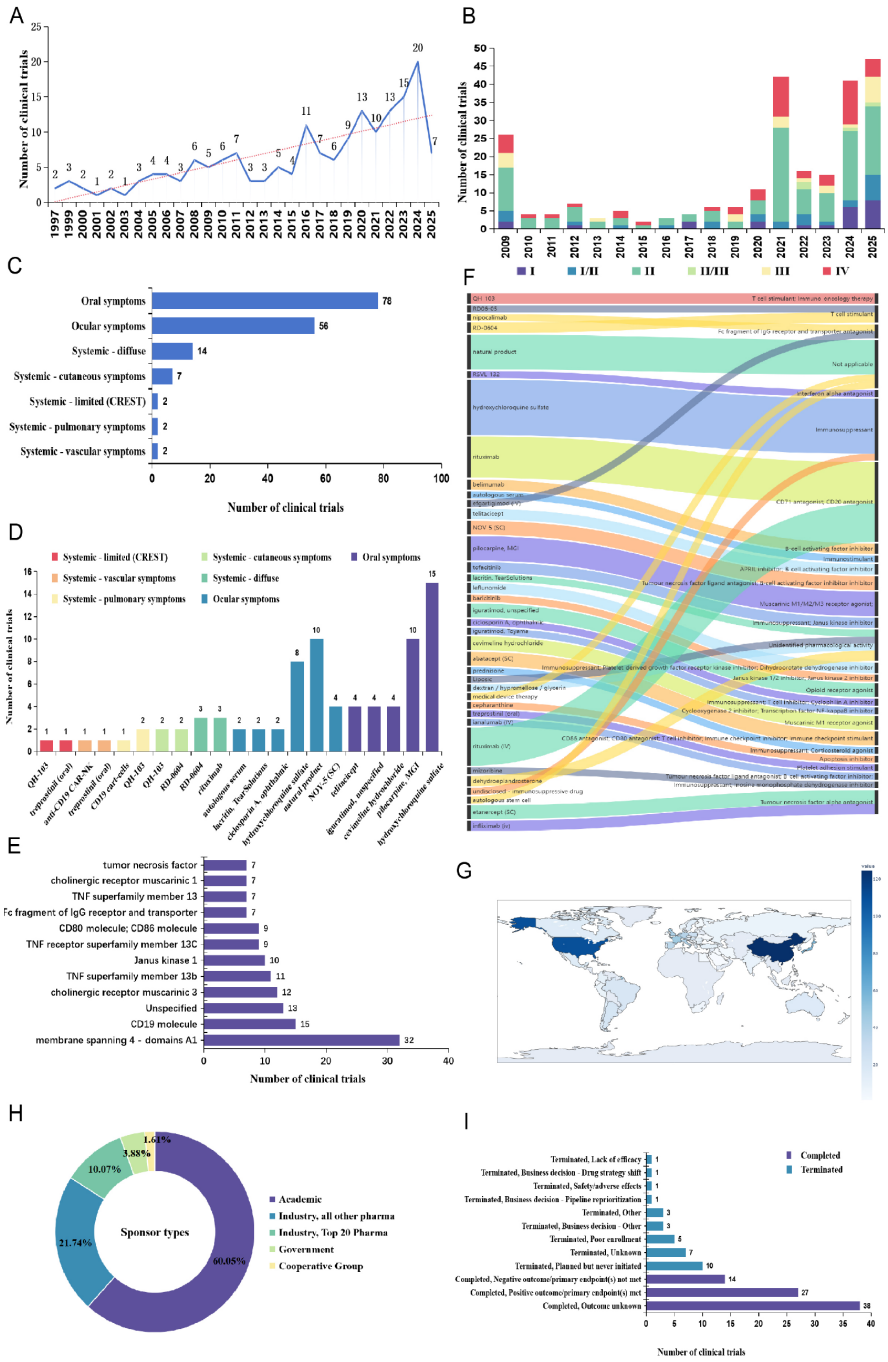

Fig. 1. Analysis and trends in Sjögren's disease (SjD) clinical trials.
A: Annual number of SjD clinical trials (1997-2025). Line graph depicting the annual count of clinical trials for SjD registered in the Trialtrove database (1997-2025), illustrating trends in translational research momentum over time.
B: Phase distribution of SjD clinical trials by year (2009-2025). Stacked bar graph showing the phase distribution of SjD clinical trials per year (2009-2025). (Phase I: Early-stage trials evaluating safety and dosage in small populations; Phase I/II: Combined trials assessing safety (Phase I) and initial efficacy (Phase II); Phase II: Trials evaluating efficacy and side effects in larger patient groups; Phase II/III: Combined trials confirming efficacy (Phase II) and comparing to standard treatments (Phase III); Phase III: Large-scale trials confirming efficacy, safety, and optimal use; Phase IV: Post-marketing trials monitoring long-term safety and real-world effectiveness.)
C: Number of SjD clinical trials by target symptom domain. Bar graph displaying the number of SjD clinical trials stratified by target symptom domain: oral symptoms, ocular symptoms, systemic - diffuse, systemic - cutaneous symptoms, systemic - limited (CREST), systemic - pulmonary symptoms, and systemic - vascular symptoms. (CREST: calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasia).
D: Number of SjD clinical trials by intervention and symptom domain. Grouped bar graph illustrating the count of SjD clinical trials by intervention type and stratified by symptom domain (red: systemic, limited (CREST); orange: systemic, vascular symptoms; yellow: systemic, pulmonary symptoms; green: systemic, cutaneous symptoms; cyan: systemic, diffuse; blue: ocular symptoms; purple: oral symptoms). (HCQ: hydroxychloroquine sulfate; JAK: Janus kinase).
E: Number of SjD clinical trials by therapeutic target domain. Bar graph showing the number of SjD clinical trials targeted against key molecular entities. (TNF: tumour necrosis factor; CHRM1: cholinergic receptor muscarinic 1; CD19: a B-cell surface protein involved in B-cell activation; CD20: a B-cell surface protein encoded by the MS4A1 gene, targeted for B-cell depletion)
F: Primary tested drug and therapeutic mechanism of SjD clinical trials. Sankey diagram illustrating the flow of SjD clinical trials across two tiers: left tier: primary tested drug (*e.g.* conventional immunosuppressants, B-cell–targeted biologics, JAK inhibitors; right tier: therapeutic mechanism (*e.g.* B-cell depletion, cytokine modulation, glandular function restoration). Band width corresponds to the number of trials in each category.
G: Geographic distribution of SjD clinical trials. Choropleth map depicting the global distribution of SjD clinical trials, with colour intensity indicating the number of trials hosted by each country.
H: Sponsor types of SjD clinical trials. Pie chart showing the proportion of interventional SjD clinical trials by sponsor type: Academic (research institutions), Industry (all pharmaceutical companies except top 20), Industry (Top 20 Pharma; leading global pharmaceutical companies by revenue), Government, and Cooperative Group (multisite research consortia).
I: Trial status and outcomes of SjD clinical trials. Bar graph summarising status and outcomes of SjD clinical trials. Terminated trials are subcategorised by reason (*e.g.* lack of efficacy, business decision); completed trials are subcategorised by outcome (*e.g.* positive primary endpoint [statistically significant improvement in measures like ESSPRI (EULAR Sjögren's Syndrome Patient Reported Index) scores or salivary flow], negative primary endpoint, outcome unknown).

ly 79 trials were completed, and of those, 48.1% (38/79) showed statistically significant improvements in primary endpoints like reduced ESSPRI scores or normalised salivary flow (Fig. 1I).

The therapeutic dilemma of SjD is confirming the effectiveness of commonly used medications. Despite HCQ's frontline status, it demonstrates limited efficacy for glandular symptoms, 22.9% of trials failed primary endpoints (n=2/9), with 55.6% producing indeterminate outcomes (n=5/9) (Table I). Considering the potential retinal toxicity associated with the long-term use of HCQ, it is imperative to evaluate whether distinct subgroups of patients with SjD should persist with prolonged administration of this medication (8). Nonetheless, despite these challenges to HCQ's universal efficacy and emerging safety considerations, the existing evidence remains inconclusive, underscoring the need for larger, well-controlled trials to definitively establish the role of HCQ in SjD.

Mechanism-driven innovative drugs represent a critical breakthrough in the development of treatment strategies for SjD. Recent advances illuminate three transformative therapeutic frontiers: 1) Immune dysregulation: single-cell studies identify pathogenic CXCR5+PD-1+ Tfh-like cells in salivary glands, which drive B-cell hyperactivity via IL-21 (9); 2) Microbiome crosstalk: gut/oral dysbiosis in SjD patients exacerbates autoimmunity through molecular simulation mechanisms (10), while microbial

metabolite interventions (*e.g.* short-chain fatty acids) reduce gland inflammation in mouse models (11); 3) Gland regeneration: stem cell therapies such as induced pluripotent stem cells (iPSCs)-derived acinar cells restore salivary function in preclinical studies, and ongoing clinical trials (TrialTroveID-381840) evaluating regenerative strategies for irreversible glandular damage. These discoveries fuel a paradigm shift from symptom suppression to mechanistic intervention, prioritising immune homeostasis and gland repair. While the prospects are promising, most candidates are still in early-phase development, and their ultimate efficacy and safety profiles await confirmation in large-scale Phase III trials.

National regulatory frameworks shape therapeutic development trajectories. The FDA's "accelerated approval pathway" favouring drugs for rare diseases like SjD and China's "Strategic Plan for Traditional Chinese Medicine Development" supporting natural products may partially explain regional research preferences: the U.S. leans toward biologics, while China focuses more on small molecules, such as natural product formulations. Future efforts should strengthen cross-border data sharing and endpoint standardisation to accelerate the emergence of truly breakthrough therapies.

In conclusion, our comprehensive analysis of global clinical trials reveals pivotal advances in SjD therapeutics. Our analysis raises doubts about HCQ's role as the main treatment for SjD. The treatment strategy of SjD focuses on advancing mechanism-driven approaches, particularly targeting B-cell depletion, cytokine modulation, and glandular repair. Additionally, some emerging modalities like CAR, T and iPSC, based gland regeneration are breaking through traditional therapeutic bottlenecks. Moreover, collaborative regional research has the potential to enhance the comprehensiveness of SjD drug development and facilitate new breakthroughs. Overall, these findings highlight a shift in SjD treatments from merely suppressing symptoms to mechanism-driven oriented therapeutic strategies.

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