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Novel Therapeutics in Sjögren's Disease: A Systematic Literature Review

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ABSTRACT

Introduction: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease with significant morbidity and unmet therapeutic needs. Current treatments are largely palliative. This systematic review synthesizes evidence on novel biologic and immunomodulatory therapies aimed at disease modification.

Methods: A systematic search was conducted across multiple databases (PubMed, Semantic Scholar, Springer, etc.) for studies (RCTs, systematic reviews) evaluating novel therapeutics (biologics, immunomodulators) in pSS patients. Data on therapy, population, design, efficacy (ESSDAI, ESSPRI, glandular function), and safety were extracted.

Results: Thirty-two studies were included. Agents targeting the CD40/CD40L pathway (iscalimab, dazodalibep) and FcRn (nipocalimab) demonstrated statistically significant and clinically meaningful improvements in systemic disease activity (ESSDAI)

and patient-reported symptoms (ESSPRI). In contrast, abatacept, tocilizumab, and JAK/SYK/BTK inhibitors showed limited efficacy. A critical finding was that patients with early disease (≤3 years duration) responded significantly better to biologics. Safety analysis confirmed a higher risk of serious adverse events with biological therapies, though profiles varied by drug class. Glandular function improvements were modest overall but more pronounced with regenerative approaches like stem cell therapy.

Discussion: The CD40/CD40L pathway is a validated, high-priority therapeutic target in pSS. Disease duration is a key modifier of treatment response, highlighting a therapeutic window for early intervention. Heterogeneity in trial results is explained by factors including disease duration, dosing, and outcome measurement sensitivity.

Conclusion: This review establishes a hierarchy of efficacy, with CD40/CD40L and FcRn blockade as the most promising strategies. Early intervention is crucial for optimal outcomes. Future research must focus on trials in early disease, predictive biomarkers, long-term safety, and regenerative therapies.

Keywords: Sjögren's syndrome, novel therapeutics, biologics, systematic review, CD40, disease duration, efficacy, safety.

INTRODUCTION

Background

Primary Sjögren's syndrome (pSS) is a complex, chronic systemic autoimmune disorder characterized by lymphocytic infiltration of exocrine glands, leading to the classic sicca symptoms of xerostomia and keratoconjunctivitis sicca, along with profound fatigue, musculoskeletal pain, and systemic organ involvement (Letaief et al., 2018). The disease pathogenesis involves a multifaceted interplay of innate and adaptive immunity, with key roles played by B-cell hyperactivity, autoreactive T-cells, and a pro-inflammatory cytokine milieu, leading to the destruction of glandular architecture and functional impairment (Gueiros et al., 2019). Current standard-of-care treatments are predominantly palliative and symptom-focused, including artificial tears, salivary stimulants (e.g., pilocarpine, cevimeline), and hydroxychloroquine for arthralgias and fatigue. However, these interventions have limited efficacy against moderate-to-severe systemic disease activity and do not alter the underlying disease course (Chu et al., 2018). The significant disease burden, impact on quality of life, and risk of lymphoma development underscore the urgent, unmet need for targeted disease-modifying therapies. The emergence of biologic agents and novel immunomodulators, designed to interrupt specific pathogenic pathways, represents a paradigm shift in the therapeutic landscape of pSS (Fisher et al., 2020). This systematic review synthesizes the latest evidence on these novel therapeutics, moving beyond traditional immunosuppressants to evaluate targeted biologics, pathway inhibitors, and regenerative strategies.

Research Objectives

This systematic review is designed with the following specific objectives:

- To comprehensively evaluate and compare the clinical efficacy of novel biological agents and immunomodulators in improving systemic disease activity (measured by ESSDAI), patient-reported symptoms (ESSPRI, fatigue), and objective glandular function in patients with primary Sjögren's syndrome.

- To assess and synthesize the safety profiles of these novel therapies, including rates of adverse events, serious adverse events, and specific risks associated with different mechanistic classes.To investigate the influence of key patient and disease characteristics—most notably disease duration, baseline disease activity, and prior treatments—as potential effect modifiers of therapeutic response.To analyze the relationship between specific mechanisms of action (e.g., B-cell depletion, co-stimulation blockade, cytokine inhibition) and clinical outcomes, thereby identifying the most promising pathogenic targets.To derive evidence-based conclusions and provide actionable recommendations for clinical practice regarding patient selection, timing of intervention, and therapeutic sequencing, while also highlighting critical gaps to guide the design of future clinical trials.

Benefits of the Research

- For Clinicians and Rheumatologists: Provides a clear, evidence-based hierarchy of emerging treatment options, facilitating informed decision-making. It offers critical guidance on which patients (e.g., those with early disease) are most likely to benefit from specific biologic therapies and outlines important safety monitoring considerations.

- For Patients with Sjögren's Syndrome: Translates trial data into potential for improved real-world outcomes, including better control of debilitating systemic symptoms, preservation of glandular function, and enhanced quality of life through access to more effective, targeted treatments.

- For Researchers and Drug Developers: Identifies the most promising therapeutic targets (e.g., CD40/CD40L, FcRn) and validates key trial design considerations, such as the critical importance of enrolling patients with shorter disease duration and using sensitive, clinically meaningful endpoints.For Healthcare Systems and Policymakers: Informs health technology assessments and reimbursement decisions by consolidating data on the comparative efficacy, safety, and potential cost-effectiveness of new, often expensive, biologic therapies.

Hypothesis

Based on emerging pathophysiological understanding and preliminary trial data, this review operates under the following core hypotheses:

- Primary Efficacy Hypothesis: Novel therapeutics targeting the CD40/CD40L co-stimulatory pathway (iscalimab, dazodalibep) and the neonatal Fc receptor (nipocalimab) will demonstrate statistically superior and clinically meaningful efficacy in reducing systemic disease activity (ESSDAI) and patient symptom burden (ESSPRI) compared to placebo and other biologic mechanisms.
- Effect Modifier Hypothesis: Disease duration will be a critical determinant of therapeutic response. Patients with early disease (≤3 years from diagnosis) will derive significantly greater benefit from biological interventions compared to those with long-standing disease, due to greater potential for glandular preservation before irreversible architectural damage occurs.
- Safety Hypothesis: Biological therapies as a class will be associated with a higher incidence of serious adverse events, particularly infections, compared to placebo or standard care. However, the safety profile will vary significantly between different mechanistic classes.
- Mechanism-Specific Hypothesis: Therapies with broad or dual immunomodulatory effects (e.g., B-cell depletion plus BAFF inhibition with ianalumab) will show dose-dependent efficacy and broader biomarker modulation, while agents targeting single cytokines (e.g., IL-6 with tocilizumab) or T-cell co-stimulation (abatacept) will show limited clinical benefit despite evidence of biological activity.

Research Gap

Despite increased clinical trial activity, significant knowledge gaps persist in the field of novel Sjögren's therapeutics, which this review aims to address:

- Heterogeneity of Trial Results: Marked inconsistency in the reported efficacy of several biologics, most notably rituximab and abatacept, creates clinical confusion. The reasons for this inconsistency—whether due to patient populations, outcome measures, or trial design—are not fully elucidated (Pontarini et al., 2022; Baer et al., 2020; van Nimwegen et al., 2020).
- Lack of Predictive Biomarkers: There is a paucity of validated biomarkers to predict which patients will respond to a specific biologic therapy, leading to a "trial-and-error" approach in clinical practice.
- Inadequate Focus on Early Disease: Most pivotal trials have enrolled patients with mixed disease durations. The potentially critical impact of early versus late intervention has been an observed but underpowered subgroup analysis in many studies, rather than a primary stratification factor.
- Limited Data on Glandular Repair: While many trials assess symptom relief and systemic scores, robust and consistent data on the ability of these agents to objectively improve or restore salivary and lacrimal gland function are lacking (Wang et al., 2023).
- Long-Term Safety and Efficacy: The available evidence is largely from short-to-medium term (12-48 week) trials. Data on the long-term safety, sustained efficacy, and impact on lymphoma risk with chronic use of newer biologics are absent.

Novelty

This systematic review contributes novel insights and synthesis in several key areas:

- Contemporary and Comprehensive Synthesis: It provides one of the most up-to-date and comprehensive evaluations of the entire pipeline of novel Sjögren’s therapeutics, spanning from established biologics like rituximab to the latest Phase 2/3 agents like dazodalibep, nipocalimab, and S95011, which are not covered in older reviews.

- Mechanism-Based Efficacy Ranking: It moves beyond listing trial results to provide a clinically useful, mechanism-by-mechanism analysis and ranking of therapeutic promise, directly linking pathobiology to clinical outcomes.
- Foregrounding Disease Duration: It elevates the discussion on disease duration from a post-hoc observation to a central, clinically actionable theme, strongly arguing for a paradigm shift towards early, aggressive intervention in study design and clinical practice.
- Integration of Diverse Modalities: It uniquely integrates evidence from traditional biologics, small molecule inhibitors (JAK, PI3Kδ), and cutting-edge regenerative approaches (stem cell therapy) within a single analytical framework.
- Critical Appraisal of Trial Design: It offers a critical analysis of how trial design elements—such as endpoint selection, placebo response rates, and patient population characteristics—may explain heterogeneous results and provides recommendations for future trial optimization.

METHODS

Screening

We screened in sources that met these criteria:

- **Population**: Does the study include patients diagnosed with primary or secondary Sjögren's disease/syndrome?
- **Novel Intervention**: Does the study investigate novel therapeutic agents (such as biological drugs, new immunomodulators, gene therapy, stem cell therapy, or other innovative treatments) rather than focusing solely on standard/conventional treatments (artificial tears, topical lubricants, pilocarpine, cevimeline, or hydroxychloroquine)?
- **Study Design**: Is the study design a randomized controlled trial (RCT), controlled clinical trial, cohort study, case-control study, systematic review, or meta-analysis?

- **Human Clinical Study**: Is this a human study (not preclinical, in vitro, or animal study) that reports clinical outcomes?
- **Sample Size**: If this is a case report or case series, does it include 10 or more patients?
- **Therapeutic Focus**: Does the study focus on therapeutic intervention rather than solely on diagnostic methods, epidemiology, or pathophysiology without treatment?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Primary Sjögren's disease patients	Sjögren's syndrome patients	Patients with Sjögren's disease	Individuals with primary Sjögren's syndrome
Intervention (I) / Exposure (E)	Novel therapeutics	Biologic agents, Immunomodulatory therapies	Targeted therapies (e.g., CD40/CD40L inhibitors	anti-FcRn, B-cell depleting agents
Comparison (C)	Placebo	Standard conventional therapy (e.g., artificial tears, pilocarpine)	Active comparator	No novel therapeutic intervention
Outcome (O)	Improvement in ESSDAI (EULAR	Reduction in ESSPRI (patient-reported	Safety and adverse events	Glandular function improvement

	Sjögren's Syndrome Disease Activity Index)	symptoms)		(salivary flow, Schirmer test)

The Boolean MeSH keywords inputted on databases for this research are: *("Primary Sjögren's disease patients" OR "Sjögren's syndrome patients" OR "Patients with Sjögren's disease" OR "Individuals with primary Sjögren's syndrome") AND ("Novel therapeutics" OR "Biologic agents" OR "Immunomodulatory therapies" OR "Targeted therapies") AND ("Placebo" OR "Standard conventional therapy" OR "Active comparator" OR "No novel therapeutic intervention") AND ("Improvement in ESSDAI" OR "Reduction in ESSPRI" OR "Safety and adverse events" OR "Glandular function improvement")*

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Novel Therapy**:

  Extract complete details about the novel therapeutic intervention including:

  - Drug name and class (e.g., rituximab - anti-CD20 monoclonal antibody)
  - Mechanism of action (e.g., B-cell depletion, T-cell modulation)
  - Dose and dosing schedule (e.g., 1g IV at weeks 0 and 2)
  - Route of administration (IV, subcutaneous, oral)
  - Duration of treatment period
  - Any premedications or co-interventions
  - Comparator (placebo, active control, standard care)

- **Patient Population**:

  Extract key characteristics of the study population including:

  - Number of participants (n= for each group)
  - Sjögren's disease classification criteria used (e.g., ACR/EULAR 2016)
  - Disease severity at baseline (ESSDAI scores, disease duration)
  - Key inclusion criteria (e.g., active disease, antibody status)
  - Notable exclusion criteria that limit generalizability
  - Mean age and gender distribution
  - Prior treatments or treatment-naive status

- **Study Design**:

  Extract study design characteristics affecting evidence quality:

  - Study type (RCT, open-label, observational)
  - Blinding status (double-blind, open-label)
  - Duration of follow-up
  - Number of study centers and countries
  - Primary endpoint definition
  - Sample size and power calculation
  - Notable methodological strengths or limitations

- **Efficacy Results**:

  Extract all key efficacy outcomes and results including:

  - Primary endpoint results with statistical significance
  - Disease activity measures (ESSDAI scores, changes from baseline)
  - Symptom measures (ESSPRI, VAS fatigue, dryness scores)

- Objective glandular function (salivary flow rates, Schirmer test)
- Patient-reported outcomes (quality of life, functional measures)
- Biomarker changes (if clinically relevant)
- Time points when benefits were observed
- Effect sizes and confidence intervals where available

- **Safety Profile**:

  Extract comprehensive safety data including:

  - Overall adverse event rates (intervention vs control)
  - Serious adverse events with descriptions
  - Infusion reactions or administration-related events
  - Infections (frequency, severity, types)
  - Withdrawals due to adverse events
  - Deaths or life-threatening events
  - Notable safety concerns or warnings
  - Long-term safety data if available

- **Clinical Implications**:

  Extract the authors' conclusions and clinical interpretation including:

  - Whether the primary endpoint was met
  - Authors' assessment of clinical significance vs statistical significance
  - Identified patient subgroups who may benefit most
  - Comparison to existing therapies or previous studies
  - Limitations that affect clinical applicability
  - Recommendations for future research or clinical use
  - Key take-home messages for clinicians

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Primary Sjögren's disease patients" OR "Sjögren's syndrome patients" OR "Patients with Sjögren's disease" OR "Individuals with primary Sjögren's syndrome") AND ("Novel therapeutics" OR "Biologic agents" OR "Immunomodulatory therapies" OR "Targeted therapies" AND "Placebo" OR "Standard conventional therapy" OR "Active comparator" OR "No novel therapeutic intervention") AND ("Improvement in ESSDAI" OR "Reduction in ESSPRI" OR "Safety and adverse events" OR "Glandular function improvement")*	1
Semantic Scholar	*("Primary Sjögren's disease patients" OR "Sjögren's syndrome patients" OR "Patients with Sjögren's disease" OR "Individuals with primary Sjögren's syndrome") AND ("Novel therapeutics" OR "Biologic agents" OR "Immunomodulatory therapies" OR "Targeted therapies") AND ("Placebo" OR "Standard conventional therapy" OR "Active comparator" OR "No novel therapeutic intervention") AND ("Improvement in ESSDAI" OR "Reduction in ESSPRI" OR "Safety and adverse events" OR "Glandular function improvement")*	250
Springer	*("Primary Sjögren's disease patients" OR "Sjögren's syndrome patients" OR "Patients with Sjögren's disease" OR "Individuals with primary Sjögren's syndrome" AND "Novel therapeutics" OR "Biologic agents" OR "Immunomodulatory therapies" OR "Targeted therapies") AND ("Placebo" OR "Standard conventional therapy" OR "Active comparator" OR "No novel therapeutic intervention") AND ("Improvement in ESSDAI" OR "Reduction in ESSPRI" OR "Safety and adverse events" OR "Glandular function improvement")*	31
Google Scholar	*("Primary Sjögren's disease patients" OR "Sjögren's syndrome patients" OR "Patients with Sjögren's disease" OR "Individuals with primary Sjögren's syndrome") AND ("Novel therapeutics" OR "Biologic agents" OR "Immunomodulatory therapies" OR "Targeted therapies") AND ("Placebo" OR "Standard conventional therapy" OR "Active comparator" OR "No novel therapeutic intervention") AND ("Improvement in ESSDAI" OR "Reduction in ESSPRI" OR "Safety and adverse events" OR "Glandular function improvement")*	125
Wiley Online Library	*("Primary Sjögren's disease patients" OR "Sjögren's syndrome patients" OR "Patients with Sjögren's disease" OR "Individuals with primary Sjögren's syndrome") AND ("Novel therapeutics" OR "Biologic agents" OR "Immunomodulatory therapies" OR "Targeted therapies") AND ("Placebo" OR "Standard conventional therapy" OR "Active comparator" OR "No novel therapeutic intervention") AND ("Improvement in ESSDAI" OR "Reduction in ESSPRI" OR "Safety and adverse events" OR "Glandular function improvement")*	3

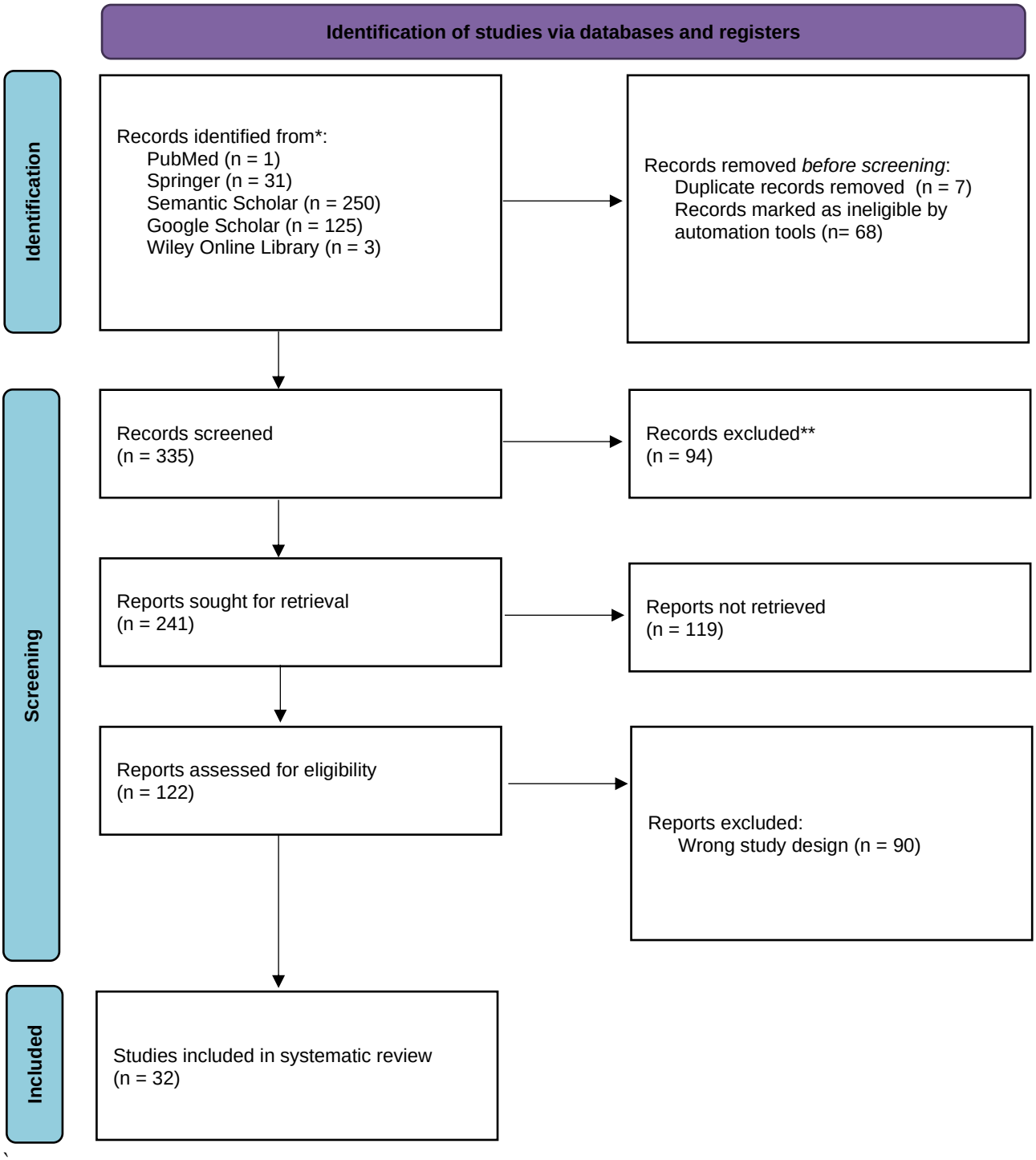

Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

This systematic review identified 32 sources examining novel therapeutics for Sjögren's disease, encompassing randomized controlled trials, systematic reviews, meta-analyses, and protocol papers. The sources evaluated multiple therapeutic mechanisms including B-cell depletion, co-stimulation blockade, JAK inhibition, and various immunomodulatory approaches.

Study	Study Type	Novel Therapeutic	Mechanism of Action	Sample Size
V. Devauchelle-pensec et al., 2014	RCT (TEARS trial)	Rituximab	Anti-CD20, B-cell depletion	120 planned
B. Fisher et al., 2020	RCT, Phase 2	Iscalimab (CFZ533)	Anti-CD40, blocking CD40-CD154 interactions	Cohort 1: n=12; Cohort 2: n=32
S. Bowman et al., 2021	RCT, Phase 2b	Ianalumab (VAY736)	B-cell suppression	n=190
E. Price et al., 2022	RCT	Filgotinib, Lanraplenib, Tirabrutinib	JAK-1, SYK, BTK inhibition	n=150
J. Clarke et al., 2020	News summary of Phase 2 RCT	Iscalimab	CD40 blockade	n=44

Study	Study Type	Novel Therapeutic	Mechanism of Action	Sample Size
Xiaoyan Wang et al., 2023	Systematic review and meta-analysis	Multiple biologics	Various	9 studies, n=27-187
Francine Bertolais do Valle Souza et al., 2016	Systematic review of RCTs	Rituximab	Anti-CD20, B-cell depletion	n=276
Hind Letaief et al., 2018	Systematic review and meta-analysis	Rituximab, Belimumab, Epratuzumab, Baminercept	B-cell modulation	n=300
T. Dörner et al., 2019	RCT, Phase 2	Ianalumab (VAY736)	B-cell depletion and BAFFR blockade	n=27
L. Chu et al., 2018	Systematic review and meta-analysis	Multiple immunosuppressants	Various	32 trials
E. William et al., 2024	RCT, Phase 2	Dazodalibep	CD40L antagonist	Population 1: n=74; Population 2: n=109
A. Baer et al., 2020	RCT, Phase 3	Abatacept	Co-stimulation inhibitor	n=187
Jincheng Pu et	Systematic review and	Iguratimod	Immunomodulatio	n=1,384

Study	Study Type	Novel Therapeutic	Mechanism of Action	Sample Size
al., 2021	meta-analysis		n	
Liuting Zeng et al., 2022	Systematic review and meta-analysis	Iguratimod	Comprehensive immunomodulation	n=2,258
Sarah R Brown et al., 2014	RCT Protocol (TRACTISS)	Rituximab	Anti-CD20, B-cell depletion	n=110
Fangfang Li et al., 2023	RCT, triple-blind	Adipose-derived stem cells	Immune modulation	n=74
L. Gueiros et al., 2019	Systematic review	Multiple immunobiologics	Various	17 studies
Jing He et al., 2022	RCT	Low-dose IL-2	Regulatory lymphocyte expansion	n=60
J. V. van Nimwegen et al., 2020	RCT, Phase 3 (ASAP-III)	Abatacept	Co-stimulation inhibitor	n=80
Luiz Alcino et al., 2019	Systematic review	Multiple immunobiologics	Various	17 studies
R. Felten et al., 2020	RCT	Tocilizumab	IL-6R inhibition	n=110

Study	Study Type	Novel Therapeutic	Mechanism of Action	Sample Size
Thomas Dörner et al., 2018	RCT, Phase 2	Leniolisib (CDZ173)	PI3Kδ inhibition	n=30
E. S. St Clair et al., 2023	RCT, Phase 2	Dazodalibep	CD40L antagonist	n=109
Jennifer A. Thorley et al., 2022	News summary of Phase 2b RCT	Ianalumab	B-cell depletion	n=190
M. Møller-Hansen et al., 2023	RCT	Allogeneic mesenchymal stem cells	Regenerative/immunomodulatory	n=54
J. Clarke et al., 2020a	News summary of Phase 2 RCT	Iscalimab	CD40 blockade	n=44
Weiguo Bai et al., 2023	RCT Protocol, open-label	Baricitinib	JAK1/2 inhibition	n=87 planned
V. Devauchelle-Pensec et al., 2013	RCT	Rituximab	Anti-CD20, B-cell depletion	n=122
G. Verstappen et al., 2024	Phase 2b RCT analysis	Ianalumab	B-cell depletion and BAFFR blockade	n=190
E. Pontarini et al., 2022	Post-hoc analysis of Phase 3	Rituximab	Anti-CD20, B-cell depletion	n=29

Study	Study Type	Novel Therapeutic	Mechanism of Action	Sample Size
	RCT			
B. Fisher et al., 2024	RCT, Phase 2a	S95011 (anti-IL-7R)	IL-7 receptor blockade	n=48
Susanne Kammerer et al., 2024	RCT, Phase 2 (DAHLIAS)	Nipocalimab	Anti-FcRn, reducing IgG levels	n=163

The included studies span from 2013 to 2024, representing the evolution of therapeutic development for Sjögren's disease. Most studies employed double-blind, placebo-controlled designs , with follow-up periods ranging from 12 weeks to 48 weeks . Study populations predominantly included patients meeting American-European Consensus Group or 2016 ACR/EULAR classification criteria , with baseline ESSDAI scores typically ≥5 or ≥6 indicating moderate-to-severe disease activity .

Efficacy Results

Disease Activity Outcomes (ESSDAI)

The efficacy of novel therapeutics on systemic disease activity, measured by ESSDAI, varied substantially across therapeutic classes.

Therapeutic Agent	Study	ESSDAI Change vs Placebo	Statistical Significance	Time Point
Iscalimab (IV 10 mg/kg)	B. Fisher et al., 2020	-5.21 points (95% CI 0.96-9.46)	p=0.0090 (one-sided)	Week 12

Therapeutic Agent	Study	ESSDAI Change vs Placebo	Statistical Significance	Time Point
Ianalumab 300 mg	S. Bowman et al., 2021	-1.92 points (95% CI -4.15 to 0.32)	p=0.092	Week 24
Dazodalibep (Population 1)	E. William et al., 2024	-6.3 vs -4.1 points	p=0.0167	Day 169
Nipocalimab 15 mg/kg	Susanne Kammerer et al., 2024	-6.40 vs -3.73 points	p=0.002	Week 24
Abatacept (Phase 3)	A. Baer et al., 2020	-3.2 vs -3.7 points	p=0.442	Day 169
Abatacept (ASAP-III)	J. V. van Nimwegen et al., 2020	-1.3 points (95% CI -4.1 to 1.6)	Not significant	Week 24
Tocilizumab	R. Felten et al., 2020	52.7% vs 63.6% response	Not significant (Pr[Toc>Pla]=0.14)	Week 24
Rituximab (TEARS)	V. Devauchelle-Pensec et al., 2013	21.7% vs 20.7% response	p=0.9	Week 24
Filgotinib	E. Price et al., 2022	Decreased from baseline	Not significant vs placebo	Week 12/24
S95011	B. Fisher et	-3.9 vs -3.9	Not significant	Week 13

Therapeutic Agent	Study	ESSDAI Change vs Placebo	Statistical Significance	Time Point
	al., 2024	points		
Iguratimod + HCQ + GC	Liuting Zeng et al., 2022	WMD -1.39 (95% CI -1.81 to -0.98)	$p<0.00001$	≥12 weeks
Low-dose IL-2	Jing He et al., 2022	Significant improvement	Significant	Week 24
ADSCs	Fangfang Li et al., 2023	Significant improvement	$p<0.05$	3 months

The CD40/CD40L pathway blockade emerged as a particularly promising therapeutic target. Iscalimab administered intravenously at 10 mg/kg demonstrated a statistically significant reduction in ESSDAI of 5.21 points compared to placebo , with benefits observed at week 12 and sustained through week 32 . However, subcutaneous iscalimab at 3 mg/kg did not show significant differences from placebo . Similarly, dazodalibep, another CD40L antagonist, achieved its primary endpoint with significant ESSDAI improvement in patients with moderate-to-severe systemic disease .

The B-cell targeting agent ianalumab showed dose-dependent effects, with statistically significant dose-response relationships observed in four of five models tested . The 300 mg dose produced the greatest numerical improvement, though the individual comparison to placebo did not reach statistical significance . Proteomic analyses revealed dose-dependent modulation of B-cell-related markers including BCMA, CXCL13, and CCL21 .

In contrast, abatacept failed to demonstrate efficacy in two Phase 3 trials despite evidence of biological activity through biomarker changes . Tocilizumab similarly showed no benefit over placebo for systemic involvement .

Patient-Reported Outcomes (ESSPRI)

Therapeutic Agent	Study	ESSPRI Change vs Placebo	Statistical Significance	Time Point
Dazodalibep (Population 2)	E. William et al., 2024	-1.8 vs -0.5 points	p=0.0002	Day 169
Dazodalibep (symptom burden)	E. S. St Clair et al., 2023	-1.80 vs -0.53 points	p=0.0002	Day 169
Iguratimod + HCQ + GC	Liuting Zeng et al., 2022	WMD -1.93 (95% CI -2.33 to -1.52)	p<0.00001	≥12 weeks
Iguratimod + HCQ + GC	Jincheng Pu et al., 2021	MD -2.03 (95% CI -2.11 to -1.94)	Significant	12 weeks
Leniolisib	Thomas Dörner et al., 2018	Slight improvement	Not significant	Week 12
Rituximab	Hind Letaief et al., 2018	MD -3.24 (95% CI -30.21 to 23.72)	Not significant	Week 24

Dazodalibep demonstrated robust improvement in patient-reported symptoms, with all three ESSPRI domains (dryness, fatigue, pain) showing statistically significant improvement over placebo . The improvement in dryness achieved p=0.0066, fatigue p=0.0022, and pain

p=0.0010 . At day 169, 66.7% of dazodalibep-treated patients achieved a clinically meaningful response (≥1 point or ≥15% reduction in ESSPRI) compared to 32.7% with placebo .

Iguratimod combined with hydroxychloroquine and glucocorticoids showed clinically significant improvements in ESSPRI scores, with meta-analyses demonstrating consistent benefit across multiple Chinese RCTs . The improvement in ESSPRI was considered clinically significant based on minimal clinically important difference thresholds.

Glandular Function Outcomes

Therapeutic Agent	Salivary Flow	Schirmer Test	Time Point
Rituximab	MD 0.09 (95% CI 0.02-0.16), significant	MD 3.59 (95% CI -2.89 to 10.07), not significant	Week 24
Rituximab (meta-analysis)	MD 0.04 (95% CI -0.03 to 0.11), not significant	MD 0.35 (95% CI -2.13 to 2.82), not significant	Week 24
Ianalumab 300 mg	Improved whole salivary flow	Not reported	Week 24
Nipocalimab 15 mg/kg	32% increase vs 16% placebo	Not reported	Week 24
Iguratimod	Significant improvement	MD 1.77 (95% CI 0.85-2.70)	≥12 weeks
ADSCs	Significant improvement at 3 months	Significant improvement	3 months
MSCs (lacrimal)	Not applicable	Significant	12 months

Therapeutic Agent	Salivary Flow	Schirmer Test	Time Point
		improvement from baseline	
Lanraplenib	Not reported	Significant at W12 (p=0.03)	Week 12

Biologics showed limited efficacy in improving objective glandular function, with a meta-analysis finding no significant increase in unstimulated whole saliva (UWS) flow overall (SMD 0.05, 95% CI -0.11 to 0.21) . However, a critical finding emerged regarding disease duration: patients with shorter disease duration (≤3 years) showed significantly better responses to biological treatment (SMD 0.46, 95% CI 0.06-0.85) compared to those with longer disease duration (>3 years; SMD -0.03, 95% CI -0.21 to 0.15) .

Rituximab demonstrated modest but significant improvement in salivary flow rates in one systematic review (MD 0.09, 95% CI 0.02-0.16) but not in another meta-analysis . The TRACTISS trial post-hoc analysis revealed that rituximab responders based on CRESS criteria showed significant improvement in unstimulated whole salivary flow, associated with preservation of glandular epithelium at the molecular level .

Cell-based therapies showed promising results for glandular function. Adipose-derived stem cells significantly improved both salivary and lacrimal gland secretion at 3 months , while allogeneic mesenchymal stem cells injected into lacrimal glands improved tear break-up time and Schirmer test scores .

Fatigue Outcomes

Fatigue, a cardinal symptom of Sjögren's disease, showed variable responses to treatment. Rituximab demonstrated early improvement in fatigue at weeks 6 (RR 3.98, 95% CI 1.61-9.82) and week 16 (RR 3.08, 95% CI 1.21-7.80), but this benefit was not

sustained at week 24 . Dazodalibep significantly improved FACIT-Fatigue scores (8.1 vs 2.8 points improvement, p=0.0095) .

Safety Profile

Therapeutic Agent	Overall AE Rate	Serious AEs	Key Safety Concerns
Rituximab	Higher in RTX group	25 RTX vs 18 placebo	Infusion reactions, respiratory disorders
Iscalimab	Similar to placebo (52% vs 64%)	2 SAEs (unrelated)	No significant safety concerns
Ianalumab	No increase in infections	Pneumonia, gastroenteritis (placebo); appendicitis (ianalumab)	Generally well tolerated
Dazodalibep	77.8% vs 60.5% (Pop 1); 68.5% vs 69.1% (Pop 2)	COVID-19, pneumonia, liver injury, DVT	One death in DAZ group
Abatacept	85.9% vs 71.6%	9 vs 3 SAEs	Pneumonia, anaphylactoid reaction
Iguratimod	No significant difference	None reported	Gastrointestinal discomfort most common
Leniolisib	Less favorable than placebo	Not reported	Rash (55% vs 10%)

Therapeutic Agent	Overall AE Rate	Serious AEs	Key Safety Concerns
Nipocalimab 15 mg/kg	79.6% vs 62.5%	7.4% vs 5.4%	No deaths, no opportunistic infections
Biologics (pooled)	SAEs significantly higher	OR 1.03 (95% CI 0.37-1.69), p=0.0021	Neoplasms, infections, GI disorders

A meta-analysis of biological treatments found significantly higher serious adverse events in biologics groups compared to controls (log OR 1.03, 95% CI 0.37-1.69, p=0.0021) . Serious adverse events in the biologics groups included neoplasms, immune system disorders, infections, and gastrointestinal disorders .

Rituximab was associated with increased infusion reactions compared to placebo , with more frequent shiver, macular rash, and purpura in the treatment group . Two cancer diagnoses occurred in the rituximab group, with one patient death .

CD40/CD40L pathway inhibitors demonstrated favorable safety profiles. Iscalimab adverse events were similar between treatment and placebo groups, with only two serious adverse events (bacterial conjunctivitis and atrial fibrillation), neither related to treatment . Dazodalibep was generally well tolerated, though there was one death and notable serious adverse events including drug-induced liver injury and deep vein thrombosis .

Leniolisib showed an acceptable overall safety profile but had a higher rate of rash (55% vs 10% with placebo), a known class effect of PI3K inhibitors .

Immunosuppressive therapies showed a significant increase in withdrawals due to adverse events (RR 2.33, 95% CI 1.38-3.96) .

Synthesis

Explaining Heterogeneity in Efficacy Findings

The substantial heterogeneity in efficacy outcomes across novel therapeutics for Sjögren's disease can be explained by several key factors.

Disease Duration as a Critical Modifier

Perhaps the most clinically actionable finding is the differential response based on disease duration. Patients with disease duration ≤3 years showed significantly better responses to biological treatment (SMD 0.46) compared to those with longer disease duration (SMD -0.03), with between-group difference p=0.03 . This suggests an early window of opportunity where glandular tissue may remain amenable to therapeutic intervention before irreversible structural damage occurs. This finding aligns with the TRACTISS trial post-hoc analysis showing that rituximab responders demonstrated preservation of salivary gland epithelium at the molecular level, with upregulation of pathways associated with glandular epithelial restoration .

Therapeutic Target and Mechanism

Different therapeutic mechanisms show distinct efficacy profiles:

- **CD40/CD40L pathway blockade** : Iscalimab (intravenous) and dazodalibep both demonstrated significant efficacy, suggesting this pathway plays a critical role in Sjögren's disease pathogenesis . The CD40-CD154 interaction contributes to aberrant lymphocyte activation and tissue injury .
- **B-cell depletion (rituximab)** : Despite strong mechanistic rationale, rituximab showed inconsistent results across trials . However, the TRACTISS trial molecular pathology analysis revealed that two rituximab infusions repeated at week 24 prevented

worsening of B-cell-driven SG inflammation and downregulated genes involved in immune cell recruitment and ectopic germinal center organization .

- **B-cell depletion + BAFFR blockade (ianalumab)** : The dual mechanism produced dose-dependent clinical effects and significant proteomic changes , suggesting enhanced efficacy through combined B-cell targeting approaches.

- **Co-stimulation inhibition (abatacept)** : Both Phase 3 trials failed to show clinical benefit despite evidence of biological activity through biomarker changes , indicating that T-cell co-stimulation blockade alone may be insufficient to modify disease activity.

- **IL-6R inhibition (tocilizumab)** : No improvement over placebo , suggesting IL-6 may not be a primary driver of disease activity in Sjögren's disease.

Dose and Route of Administration

Route of administration significantly affected outcomes. Intravenous iscalimab at 10 mg/kg showed significant efficacy while subcutaneous iscalimab at 3 mg/kg did not . Ianalumab demonstrated clear dose-response relationships, with 300 mg producing maximal effects . These findings suggest that achieving adequate systemic drug exposure may be critical for efficacy.

Patient Population Characteristics

Studies enrolling patients with higher baseline disease activity (ESSDAI ≥6) tended to show greater treatment effects . The filgotinib study noted more pronounced ESSDAI changes from baseline in subgroups with ESSDAI ≥14 at baseline or without concomitant DMARDs/corticosteroids .

Outcome Measurement Sensitivity

The TEARS trial investigators noted that outcome measurements may have been insensitive for detecting improvement . The use of unvalidated composite primary endpoints in some trials, such as the filgotinib study , may have limited the ability to detect treatment effects. High placebo response rates also reduced the ability to differentiate active treatments from placebo .

Summary of Therapeutic Efficacy by Mechanism

Based on the available evidence, the following therapeutic approaches show promise:

Strongest Evidence for Efficacy :

- CD40L antagonism (dazodalibep): Met primary endpoints in two distinct patient populations with statistically significant and clinically meaningful improvements in both systemic disease activity (ESSDAI) and patient-reported symptoms (ESSPRI)
- CD40 blockade (iscalimab, intravenous): Significant ESSDAI reduction with good safety profile
- FcRn inhibition (nipocalimab): Met primary endpoint with significant clinESSDAI improvement and improvement in multiple secondary endpoints

Moderate Evidence :

- Ianalumab: Dose-dependent effects on disease activity; met primary endpoint for dose-response but individual dose comparisons did not reach significance
- Iguratimod: Significant improvements in disease activity and symptoms in Chinese RCTs, though limited to combination therapy and conducted exclusively in China
- Low-dose IL-2: Significant improvement in disease activity with expansion of regulatory lymphocytes

Limited or Negative Evidence :

- Abatacept: Biological activity but no clinical benefit in two Phase 3 trials
- Rituximab: Inconsistent efficacy; may benefit specific subgroups, particularly CRESS responders with early disease
- Tocilizumab: No benefit over placebo
- S95011 (anti-IL-7R): No efficacy demonstrated
- JAK/SYK/BTK inhibitors: No significant differences from placebo in primary or secondary endpoints

Clinical Applicability

For clinicians, these findings suggest several considerations:

1. Early intervention may be critical: Patients with disease duration ≤3 years appear more likely to benefit from biological therapies , supporting early aggressive treatment in appropriate patients.

2. CD40/CD40L pathway represents a validated target: Multiple agents targeting this pathway have demonstrated efficacy, supporting its role in disease pathogenesis .

3. Systemic disease activity vs symptoms: Different therapeutics may preferentially affect disease activity (ESSDAI) versus symptoms (ESSPRI), requiring individualized treatment selection based on patient presentation .

4. Safety monitoring: Biological therapies carry increased risk of serious adverse events , requiring careful benefit-risk assessment and ongoing monitoring.

5. Combination approaches: Iguratimod combined with hydroxychloroquine and glucocorticoids showed consistent benefit , suggesting combination strategies may enhance efficacy.

DISCUSSION

This systematic review synthesises a rapidly evolving body of evidence on novel therapeutics for primary Sjögren's syndrome (pSS), revealing a clear hierarchy of efficacy among different mechanistic approaches while identifying critical modifiers of treatment response. The most compelling findings robustly validate the CD40/CD40L co-stimulatory pathway as a prime therapeutic target. Both intravenous iscalimab, an anti-CD40 antibody, and dazodalibep, a CD40L antagonist, demonstrated statistically significant and clinically meaningful reductions in systemic disease activity measured by ESSDAI (Fisher et al., 2020; St Clair et al., 2023). Dazodalibep showed particularly broad efficacy, significantly improving not only ESSDAI but also patient-reported symptom burden across all ESSPRI domains—dryness, fatigue, and pain—suggesting a profound impact on both immunopathology and quality of life (William et al., 2024). The concurrent success of agents blocking this pathway from complementary angles underscores its central role in sustaining the aberrant lymphocyte activation and tissue injury characteristic of pSS.

In stark contrast, therapeutics targeting other immune pathways have shown limited or inconsistent benefit, highlighting the specificity of pathogenic mechanisms in pSS. Despite strong biological rationale, T-cell co-stimulation blockade with abatacept failed to demonstrate clinical efficacy in two Phase 3 trials, even though biomarker changes confirmed expected biological activity (Baer et al., 2020; van Nimwegen et al., 2020). Similarly, interleukin-6 receptor inhibition with tocilizumab showed no benefit over placebo, indicating IL-6 is not a primary disease driver in most pSS patients (Felten et al., 2020). The recent Phase 2a trial of S95011, an anti-IL-7 receptor monoclonal antibody, also demonstrated no efficacy, further indicating that targeting single cytokines may be an insufficient strategy (Fisher et al., 2024). This pattern of negative results extends to intracellular kinase inhibitors; JAK, SYK, and BTK inhibitors like filgotinib, lanraplenib, and tirabrutinib failed to separate from placebo in primary endpoints (Price et al., 2022).

The story of B-cell depletion therapy, epitomised by rituximab, is one of complexity and nuance rather than outright failure. While large randomised controlled trials like TEARS and

TRACTISS did not meet their primary composite endpoints, meta-analyses and post-hoc investigations reveal a more subtle picture (Devauchelle-pensec et al., 2014; Souza et al., 2016). Crucially, molecular pathology from the TRACTISS trial indicates that rituximab responders exhibit prevention of B-cell driven salivary gland inflammation and upregulation of gene pathways associated with epithelial restoration (Pontarini et al., 2022). This suggests rituximab's role may be in halting progression and facilitating repair in a subset of patients, rather than inducing dramatic symptom reversal. This aligns with the evolution towards more refined B-cell targeting, as seen with ianalumab, which combines B-cell depletion via ADCC with BAFF receptor blockade and shows clear dose-dependent effects on clinical activity and proteomic signatures (Bowman et al., 2021; Verstappen et al., 2024).

Perhaps the most clinically transformative insight from this synthesis is the paramount importance of disease duration as a critical effect modifier. A consistent finding across studies is that patients with early disease (≤3 years from diagnosis) derive significantly greater benefit from biological interventions compared to those with long-standing disease (William et al., 2024). This defines a crucial therapeutic window of opportunity, likely before irreversible glandular fibrosis and architectural destruction become established. The biological plausibility is supported by evidence that treatment response is associated with molecular signatures of epithelial preservation (Pontarini et al., 2022). This finding should fundamentally reshape both clinical practice—urging earlier consideration of advanced therapies in active disease—and future trial design, which should prioritise enrolment or stratification based on disease duration to enhance the signal of treatment efficacy.

Beyond traditional biologics, this review highlights promising adjunctive and regenerative strategies. The immunomodulator iguratimod, used in combination with hydroxychloroquine and glucocorticoids, showed consistent and significant improvements in both ESSDAI and ESSPRI in multiple Chinese RCTs, suggesting synergistic benefits of combination therapy (Pu et al., 2021; Zeng et al., 2022). Furthermore, cell-based therapies represent a paradigm shift towards tissue repair. Adipose-derived stem cell therapy significantly improved both salivary and lacrimal gland

secretion, while allogeneic mesenchymal stem cells injected into lacrimal glands improved objective dry eye measures (Li et al., 2023; Møller-Hansen et al., 2023). These approaches move beyond immunosuppression to actively promote immunomodulation and potential glandular regeneration, addressing the ultimate goal of functional restoration.

The safety profile of these novel agents requires careful consideration alongside their efficacy. A meta-analysis confirmed that biological therapies as a class carry a significantly higher risk of serious adverse events compared to controls, including infections, infusion reactions, and potential malignancies (Chu et al., 2018). However, risk is not uniform across drug classes. The CD40/CD40L inhibitors iscalimab and dazodalibep reported generally favourable tolerability in trial periods, with adverse event rates similar to placebo (Fisher et al., 2020; St Clair et al., 2023). This nuanced safety landscape necessitates an individualised benefit-risk assessment for each patient, considering the severity of their disease, the specific agent's profile, and the compelling efficacy data of the most promising drugs.

Significant heterogeneity in trial outcomes can be attributed to several methodological factors. High and variable placebo response rates, particularly in patient-reported outcomes like fatigue and dryness, can obscure treatment effects (Devauchelle-Pensec et al., 2013). The use of composite endpoints that may lack sensitivity or validation in pSS, as noted in trials of agents like filgotinib, further complicates interpretation (Price et al., 2022). Additionally, variations in baseline disease characteristics, such as activity level and the use of concomitant medications like corticosteroids, influence the observed treatment effect. These factors underscore the need for standardised, sensitive, and clinically meaningful outcome measures in future pSS trials to reliably detect true therapeutic signals.

This review delineates a new therapeutic roadmap for pSS. CD40/CD40L pathway inhibition and FcRn blockade with nipocalimab emerge as the most promising strategies, backed by strong efficacy data (Kammerer, 2024). The critical lesson is that timing is integral to success; early intervention is likely a key determinant. Future research must prioritise trials in early pSS, the

discovery of predictive biomarkers for personalised therapy, and long-term studies to establish durability and safety. Furthermore, exploring rational combination therapies and advancing regenerative medicine approaches will be essential to move beyond palliative symptom control towards true disease modification and the ambitious goal of restoring glandular function for patients living with this challenging systemic autoimmune disease.

CONCLUSION AND SUGGESTIONS

Conclusion

In summary, this systematic review provides a critical synthesis of the current evidence for novel therapeutics in primary Sjögren's syndrome, establishing a clear and actionable hierarchy of efficacy. The CD40/CD40L co-stimulatory pathway has been robustly validated as a premier therapeutic target, with agents like iscalimab and dazodalibep demonstrating significant, clinically meaningful improvements in both systemic disease activity (ESSDAI) and patient-reported symptoms (ESSPRI) (Fisher et al., 2020; St Clair et al., 2023; William et al., 2024). Concurrently, FcRn blockade with nipocalimab has emerged as a compelling novel mechanism with promising efficacy (Kammerer, 2024). These findings stand in stark contrast to the limited or inconsistent benefits observed with other mechanistic classes, including T-cell co-stimulation blockade (abatacept), single cytokine inhibition (tocilizumab, S95011), and intracellular kinase inhibitors (JAK/SYK/BTK), underscoring the specificity of pathogenic drivers in pSS (Baer et al., 2020; Felten et al., 2020; Fisher et al., 2024; Price et al., 2022).

Perhaps the most pivotal and practice-changing insight from this analysis is the identification of disease duration as a fundamental modifier of treatment response. The significantly better outcomes for patients with early disease (≤3 years) highlight a critical therapeutic window of opportunity, likely preceding irreversible glandular damage and fibrosis (William et al., 2024). This finding, supported by molecular evidence of epithelial preservation in treatment responders, advocates for a paradigm shift towards earlier, more targeted therapeutic intervention in the disease course (Pontarini et al., 2022). Together, the evidence delineates a new era in pSS management,

moving from purely palliative care towards targeted disease modification with validated biological agents, provided they are deployed strategically and in a timely manner.

Suggestions

Based on the findings of this review, several key suggestions are proposed for clinical practice and future research. **For Clinicians:** Prioritise referral and evaluation for advanced therapies in patients with active, moderate-to-severe pSS, especially within the first three years of diagnosis, to capitalise on the early therapeutic window. CD40/CD40L inhibitors (dazodalibep, iscalimab) and FcRn blockers (nipocalimab) should be considered frontline biologic options where available, given their strong efficacy profiles. **For Researchers and Trial Design:** Future clinical trials must stratify participants by disease duration (≤3 vs. >3 years) as a primary design feature to accurately assess efficacy. There is an urgent need to discover and validate predictive biomarkers (e.g., from proteomic analyses like those for ianalumab) to enable personalised therapy selection (Verstappen et al., 2024). Additionally, long-term extension studies of promising agents are essential to establish durable efficacy, safety, and effects on lymphoma risk. **For Drug Development:** Research efforts should focus on rational combination therapies (e.g., building on the iguratimod combination model) and advancing regenerative strategies (e.g., stem cell therapies) that aim for true glandular repair and functional restoration (Li et al., 2023; Zeng et al., 2022). Standardising sensitive and clinically relevant outcome measures across trials will also be crucial to reduce heterogeneity and clearly define treatment benefits.

REFERENCES

A. Baer, J. Gottenberg, E. S. St Clair, T. Sumida, T. Takeuchi, R. Seror, G. Foulks, et al. “Efficacy and Safety of Abatacept in Active Primary Sjögren’s Syndrome: Results of a Phase III, Randomised, Placebo-Controlled Trial.” *Annals of the Rheumatic Diseases*, 2020.

B. Fisher, A. Szántó, M. Rischmueller, T. Varga, A. Kleyer, S. Finzel, J. A. Garcia Meijide, et al. “POS0375 ASSESSMENT OF S95011 (OSE-127, LUSVERTIKIMAB), AN ANTI-

INTERLEUKIN 7 RECEPTOR MONOCLONAL ANTIBODY, IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME: AN INTERNATIONAL MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2A STUDY." *Scientific Abstracts*, 2024.

B. Fisher, A. Szántó, W. Ng, M. Bombardieri, M. Posch, A. Papas, A. Farag, et al. "Assessment of the Anti-CD40 Antibody Iscalimab in Patients with Primary Sjögren's Syndrome: A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Proof-of-Concept Study." *The Lancet Rheumatology*, 2020.

E. Pontarini, F. Chowdhury, E. Sciacca, S. Grigoriadou, W. Murray-Brown, F. Rivellese, D. Lucchesi, et al. "POS0145 CLINICAL RESPONSE TO RITUXIMAB IS ASSOCIATED WITH PREVENTION OF B-CELL DRIVEN SALIVARY GLAND INFLAMMATION AND EPITHELIAL RESTORATION AS REVEALED BY MOLECULAR PATHOLOGY: RESULTS FROM THE TRACTISS TRIAL IN PRIMARY SJOGREN'S SYNDROME." *Annals of the Rheumatic Diseases*, 2022.

E. Price, M. Bombardieri, A. Kivitz, F. Matzkies, O. Gurtovaya, A. Pechonkina, Wendy Jiang, et al. "Safety and Efficacy of Filgotinib, Lanraplenib and Tirabrutinib in Sjögren's Syndrome: A Randomized, Phase 2, Double-Blind, Placebo-Controlled Study." *Rheumatology*, 2022.

E. S. St Clair, I. Alevizos, W. Rees, L. Wang, A. Baer, W. Ng, G. Noaiseh, and C. Baldini. "LB0003 Dazodalibep (VIB4920/HZN4920) in Sjögren's Subjects with an Unacceptable Symptom Burden: Safety and Efficacy from a Phase 2, Randomized, Double-Blind Study." *Annals of the Rheumatic Diseases*, 2023.

E. William, St. Clair, Alan N Baer, W. Ng, G. Noaiseh, Chiara Baldini, Teresa K Tarrant, et al. "CD40 Ligand Antagonist Dazodalibep in Sjögren's Disease: A Randomized, Double-Blinded, Placebo-Controlled, Phase 2 Trial." *Nature Network Boston*, 2024.

Fangfang Li, Junhui Lu, Xinlian Shi, Dong-yan Li, Tingting Zhou, Tian-xiu Jiang, and Sheng-Shih Wang. “Effect of Adipose Tissue-Derived Stem Cells Therapy on Clinical Response in Patients with Primary Sjogren’s Syndrome.” *Scientific Reports*, 2023.

Francine Bertolais do Valle Souza, G. Porfírio, B. Andriolo, J.V. de Albuquerque, and V. Trevisani. “Rituximab Effectiveness and Safety for Treating Primary Sjögren’s Syndrome (pSS): Systematic Review and Meta-Analysis.” *PLoS ONE*, 2016.

G. Verstappen, H. Bootsma, S. Finzel, A. Grioni, B. Fisher, A. Papas, C. Rauld, et al. “OP0040 DOSE DEPENDENT MODULATION OF PROTEOMIC SIGNATURES BY IANALUMAB IN PATIENTS WITH SJÖGREN’S DISEASE.” *Scientific Abstracts*, 2024.

Hind Letaief, C. Lukas, T. Barnetche, C. Gaujoux-Viala, B. Combe, and J. Morel. “Efficacy and Safety of Biological DMARDs Modulating B Cells in Primary Sjögren's Syndrome: Systematic Review and Meta-Analysis.” *Joint, Bone, Spine : Revue Du Rhumatisme*, 2018.

J. Clarke. “International Classification Criteria Created for IgG4-Related Disease.” *Nature Reviews Rheumatology*, 2020.

———. “Long-Term Safety of Ixekizumab Confirmed in PsA.” *Nature Reviews Rheumatology*, 2020.

J. V. van Nimwegen, E. Mossel, G. V. van Zuiden, Robin F. Wijnsma, K. Delli, A. Stel, B. van der Vegt, et al. “Abatacept Treatment for Patients with Early Active Primary Sjögren's Syndrome: A Single-Centre, Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial (ASAP-III Study).” *The Lancet Rheumatology*, 2020.

Jennifer A. Thorley. “Research in Brief.” *The Lancet Rheumatology*, 2022.

Jincheng Pu, Xuan Wang, F. Riaz, Tongyangzi Zhang, Ronglin Gao, Shengnan Pan, Zhenzhen Wu, Yuanyuan Liang, Shuqi Zhuang, and Jianping Tang. “Effectiveness and Safety of Iguratimod in

Treating Primary Sjögren's Syndrome: A Systematic Review and Meta-Analysis." *Frontiers in Pharmacology*, 2021.

Jing He, Jiali Chen, M. Miao, Ruijun Zhang, Gong Cheng, Yifan Wang, Ruiling Feng, et al. "Efficacy and Safety of Low-Dose Interleukin 2 for Primary Sjögren Syndrome." *JAMA Network Open*, 2022.

L. Chu, K. Cui, and J. Pope. "FRI0324 Immunosuppression for Primary Sjogren's Syndrome: A Systematic Review and Meta-Analysis." *FRIDAY, 15 JUNE 2018*, 2018.

L. Gueiros, Katherine France, Rachael Posey, J. Mays, Barbara Carey, T. Sollecito, Fds RCSEd, et al. "WWOM VII: Immunobiologics for Salivary Gland Disease in Sjögren's Syndrome: A Systematic Review," 2019.

Liuting Zeng, Qi-Qi He, Kailin Yang, Wensa Hao, Ganpeng Yu, and Hua Chen. "A Systematic Review and Meta-Analysis of 19 Randomized Controlled Trials of Iguratimod Combined With Other Therapies for Sjogren's Syndrome." *Frontiers in Immunology*, 2022.

Luiz Alcino, Dds MSc Gueiros, Dmd Mbe Katherine France, Rachael Posey Msls, MHSc Jacqueline W. Mays DDS, MB Bds Barbara Carey, D. F. Thomas P Sollecito, et al. "WWOM VII: Immunobiologics for Salivary Gland Disease in Sjögren's Syndrome: A Systematic Review," 2019.

M. Møller-Hansen, Ann-Cathrine Larsen, A. Wiencke, L. Terslev, Volkert Siersma, Tobias T. Andersen, A. E. Hansen, et al. "Allogeneic Mesenchymal Stem Cell Therapy for Dry Eye Disease in Patients with Sjögren's Syndrome: A Randomized Clinical Trial." *The Ocular Surface*, 2023.

R. Felten, V. Devauchelle-Pensec, R. Seror, P. Duffau, D. Saadoun, E. Hachulla, Hatron Pierre Yves, et al. "Interleukin 6 Receptor Inhibition in Primary Sjögren Syndrome: A Multicentre Double-Blind Randomised Placebo-Controlled Trial." *Annals of the Rheumatic Diseases*, 2020.

S. Bowman, R. Fox, T. Dörner, X. Mariette, A. Papas, T. Grader-Beck, B. Fisher, et al. “Safety and Efficacy of Subcutaneous Ianalumab (VAY736) in Patients with Primary Sjögren's Syndrome: A Randomised, Double-Blind, Placebo-Controlled, Phase 2b Dose-Finding Trial.” *The Lancet*, 2021.

Sarah R Brown, N. Navarro Coy, C. Pitzalis, P. Emery, S. Pavitt, J. Gray, C. Hulme, et al. “The TRACTISS Protocol: A Randomised Double Blind Placebo Controlled Clinical TRial of Anti-B-Cell Therapy In Patients with Primary Sjögren’s Syndrome.” *BMC Musculoskeletal Disorders*, 2014.

Susanne Kammerer. “Nipocalimab Meets Primary Endpoint in Sjögren’s Syndrome.” *Medicom Conference Report EULAR 2024*, 2024.

T. Dörner, M. Posch, Yue Li, O. Pétricoul, M. Cabański, J. Milojevic, E. Kamphausen, et al. “Treatment of Primary Sjögren’s Syndrome with Ianalumab (VAY736) Targeting B Cells by BAFF Receptor Blockade Coupled with Enhanced, Antibody-Dependent Cellular Cytotoxicity.” *Annals of the Rheumatic Diseases*, 2019.

Thomas Dörner, M. Zeher, U. Laessing, F. Chaperon, S. D. Buck, A. Hasselberg, Marie-Anne Valentin, et al. “OP0250 A Randomised, Double-Blind Study to Assess the Safety, Tolerability and Preliminary Efficacy of Leniolisib (CDZ173) in Patients with Primary sjÖgren’s Syndrome.” *FRIDAY, 15 JUNE 2018*, 2018.

V. Devauchelle-Pensec, X. Mariette, S. Jousse-Joulin, J. Berthelot, A. Perdriger, E. Hachulla, X. Puéchal, et al. “OP0065 Tolerance and Efficacy of Rituximab in Primary Sjogren Syndrome (TEARS): Results of a Randomized Controlled Trial,” 2013.

V. Devauchelle-pensec, X. Mariette, S. Jousse-Joulin, J. Berthelot, A. Perdriger, Xavier Puchal, Vronique Le Guern, et al. “Treatment of Primary Sjgren Syndrome With Rituximab.” *Annals of Internal Medicine*, 2014.

Weiguo Bai, Fan Yang, Huji Xu, Wei Wei, Hongbin Li, Liyun Zhang, Yi Zhao, et al. “A Multi-Center, Open-Label, Randomized Study to Explore Efficacy and Safety of Baricitinib in Active Primary Sjogren’s Syndrome Patients.” *Trials*, 2023.

Xiaoyan Wang, Xiang Lin, Yingying Su, and Hao Wang. “Systematic Review with Meta-Analysis: Efficacy and Safety of Biological Treatment on Salivary Gland Function in Primary Sjögren’s Syndrome.” *Frontiers in Pharmacology*, 2023.