B-Cell Dysregulation Targeted Upstream in Primary Sjögren Disease

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Primary Sjögren disease (pSS) is a chronic autoimmune condition characterised by lymphocytic infiltration of exocrine glands, leading to sicca symptoms and systemic manifestations. Current therapeutic strategies primarily manage symptoms or target downstream inflammatory pathways, often with limited efficacy in altering disease progression. Emerging research presented at EULAR 2026 investigates upstream targeting of B-cell dysregulation, a pivotal pathological driver in pSS, aiming for earlier and more comprehensive disease modification.

KEY TAKEAWAYS

- The Pivot: Focus shifts from downstream symptom management to upstream B-cell dysregulation in primary Sjögren disease.
- The Data: Specific efficacy data (e.g., reduction in ESSDAI score, p-value) will be critical for clinical adoption.
- The Action: Clinicians should monitor for data on novel B-cell targeting agents that demonstrate disease-modifying effects beyond symptom control.

Primary Sjögren disease (pSS) is a systemic autoimmune disorder affecting approximately 0.5% of the adult population, predominantly women.1 The hallmark features include xerostomia and xerophthalmia, resulting from immune-mediated damage to salivary and lacrimal glands. Beyond sicca symptoms, patients often experience debilitating fatigue, arthralgia, myalgia, and a significant risk of developing extraglandular manifestations, including lung disease, vasculitis, and lymphoma.2 The underlying pathophysiology involves a complex interplay of genetic predisposition and environmental factors, leading to chronic activation of the innate and adaptive immune systems. B-cells play a central role in pSS pathogenesis, contributing to autoantibody production, antigen presentation, and cytokine secretion.3 Specifically, hyperactive B-cells are implicated in the formation of ectopic germinal centres within affected glands and the production of autoantibodies such as anti-Ro/SSA and anti-La/SSB, which are serological hallmarks of the disease.4

Current treatment options for pSS are largely symptomatic, including artificial tears and saliva substitutes. Immunosuppressants like hydroxychloroquine, methotrexate, and corticosteroids are used for systemic manifestations, but their efficacy in modifying the overall disease course or preventing complications remains suboptimal.5 Rituximab, a B-cell depleting agent targeting CD20, has shown mixed results in clinical trials for pSS, demonstrating some benefit in specific extraglandular manifestations but failing to meet primary endpoints for sicca symptoms in several studies.6 This limited success highlights the need for therapeutic strategies that target B-cell dysregulation more precisely or at

an earlier stage in the pathogenic cascade, moving beyond broad B-cell depletion to address specific B-cell subsets or activation pathways.

Upstream B-Cell Targeting Strategies

The EULAR 2026 presentation focuses on novel approaches to target B-cell dysregulation upstream, aiming to intervene before irreversible glandular damage or widespread systemic inflammation occurs. These strategies include agents that modulate B-cell activating factor (BAFF) or a proliferation-inducing ligand (APRIL), cytokines critical for B-cell survival, proliferation, and differentiation.7 Elevated levels of BAFF and APRIL are consistently observed in pSS patients and correlate with disease activity and autoantibody titres.8 By inhibiting these cytokines, it is hypothesised that the survival and activation of pathogenic B-cells can be curtailed, thereby reducing autoantibody production and inflammatory responses.9

One such approach involves the use of specific BAFF/APRIL inhibitors. Preclinical studies have demonstrated that blocking these pathways can reduce B-cell hyperactivity and ameliorate disease features in animal models of Sjögren disease.10 Clinical trials investigating these agents in pSS are designed to assess their impact on objective measures of disease activity, such as the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) and EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), as well as on glandular function and histological markers of inflammation.11 The rationale for upstream targeting is to prevent the full maturation and activation of pathogenic B-cells, potentially leading to a more profound and sustained therapeutic effect compared to strategies that target already activated or mature B-cells.12

The EULAR 2026 presentation is expected to detail the design and preliminary findings from trials evaluating these novel B-cell modulators. Key endpoints include changes in ESSDAI scores, improvements in salivary flow rates, ocular surface staining, and reductions in autoantibody levels. Patient populations for these trials typically include individuals with active pSS, often defined by specific ESSDAI scores or the presence of extraglandular manifestations, and seropositivity for anti-Ro/SSA or anti-La/SSB antibodies. Exclusion criteria often involve severe comorbidities or prior exposure to certain immunosuppressive biologics. Safety profiles, particularly concerning infection risk due to B-cell modulation, will also be a critical aspect of the data presented. The aim is to identify agents that can offer a disease-modifying effect, moving beyond symptomatic relief to address the core immunological pathology of pSS. The success of these upstream strategies would represent a significant advancement in the management of this complex autoimmune disease, potentially altering its natural history and improving long-term patient outcomes.13

> **CLINICAL IMPLICATIONS**
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> The persistent challenge in primary Sjögren disease has been the lack of therapies that fundamentally alter the disease course, rather than merely mitigating symptoms. The focus on upstream B-cell dysregulation, particularly through BAFF/APRIL inhibition, represents a logical evolution in therapeutic strategy. If these agents demonstrate a sustained reduction in disease activity, as measured by objective indices like ESSDAI, and crucially, an improvement in glandular function, it would necessitate a re-evaluation of current treatment algorithms. General practitioners and specialists alike should be prepared for a shift towards earlier intervention with targeted immunomodulators, potentially moving beyond the current reliance on symptomatic treatments and broad immunosuppression.

> The industry's investment in these upstream targets reflects a recognition of the unmet need in pSS. While rituximab has had a limited impact in pSS, the specificity of BAFF/APRIL inhibitors might offer a more nuanced approach, avoiding some of the broader immunosuppressive effects while still addressing the core pathology. The commercial success of such agents will hinge on clear, quantifiable benefits in hard endpoints, not just patient-reported outcomes. Payers will demand evidence of disease modification, such as prevention of lymphoma or significant reduction in extraglandular manifestations, to justify the likely premium pricing of novel biologics.
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> For patients, the prospect of a disease-modifying therapy offers hope beyond the current cycle of managing debilitating symptoms. A therapy that can preserve glandular function or prevent systemic complications would significantly improve quality of life and reduce the long-term burden of pSS. However, clinicians must temper expectations until robust, long-term safety and efficacy data are available. The history of autoimmune drug development is replete with promising early data that did not translate into widespread clinical utility. The EULAR 2026 data will be a critical step in determining whether upstream B-cell targeting truly offers a new era for primary Sjögren disease management.

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