Development of a primary Sjogren's Syndrome (pSS) quantitative systems pharmacology (QSP) model linking mechanistic pathways to clinical scores.

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Introduction: Primary Sjogren's syndrome (pSS) is a heterogeneous autoimmune disease characterized by lymphocytic infiltrates and functional impairment of exocrine glands, such as salivary and lachrymal glands, resulting in oral and ocular dryness (known as sicca syndrome). Apart from debilitating pain and fatigue, approximately 30 to 50% of patients suffer from extra-glandular manifestations due to inflammation in several organs, causing functional impairment and systemic manifestations such as adenitis, skin rash, arthritis, nephritis, pneumonitis, and neuropathy. Current pSS treatment options include symptomatic sicca therapies and broad-spectrum immunosuppression for patients with systemic manifestations.

To evaluate novel pSS drugs and optimize clinical trial outcomes, we built a novel pSS QSP model with relevant clinical trial endpoints. Evaluating pSS drugs using QSP is particularly challenging due to the variety of clinical manifestations and the complexity of the clinical scores of pSS, which involve multiple "domains". Here, we describe our strategy to link relevant pSS disease pathways in the QSP model to the various pSS domain scores and to calibrate the total pSS clinical score using published clinical data.

Objectives:

- Establish links between pSS disease pathways represented in the QSP model and components of the clinical pSS domain scores
- Calibrate the change in the pSS domain scores using published responses to biologics and standard of care (SOC) therapies

Methods: We developed the pSS PhysioPD Research Platform, a mechanistic QSP model focusing on salivary gland and lymph node manifestations in pSS. The model includes salivary gland, lymph node, and blood compartments with relevant cell types (gland epithelial cells, T and B lymphocytes, and antigen-presenting cells). Cellular activation and recruitment processes are regulated by cytokines and chemokines. The model also includes SOC drug pharmacokinetics (PK) in blood, salivary glands, and lymph nodes. The pSS Platform was qualified following Rosa's Model Qualification Method [1]. The EULAR Sjogren's syndrome disease activity index (ESSDAI) score [2] was chosen as the primary pSS clinical endpoint. Calibration of the ESSDAI domain scores were based on published clinical trial responses to the

anti-BAFFR antibody ianalumab [3] and to the leflunomide–hydroxychloroquine combination therapy (RepurpSS-I clinical trial) [4].

Results: Average pSS cell numbers and mediator concentrations in blood, lymph nodes, and salivary glands were estimated from the literature to create a representative moderate to severe virtual pSS patient (reference VP) in the Platform. Changes in tissue biomarkers upon treatment, e.g., lymph node and salivary gland volumes, pro-inflammatory mediators, and immune cell numbers were used to establish correlations between the Platform predicted outcomes and changes in the various ESSDAI domain scores (see **Table 1**). Simulations of ianalumab and SOC therapies in the Platform matched published clinical trial ESSDAI responses for both the 300-mg Q4W ianalumab-treated group and the placebo group of pSS patients [3].

Conclusion: The pSS Platform was able to predict a complex clinical score from mechanistic outputs. QSP models able to predict complex clinical endpoints, such as the ESSDAI score, facilitate communication and adoption of QSP modeling as an integral part of the drug development process by demonstrating the predictive value of quantitative tools to clinical teams.

Table 1. ESSDAI domain scores and their mapping to QSP model species.

ESSDAI domain	Domain Weight	Mapping to QSP model species
Lymphadenopathy	**4**	Based on lymph node volume
Glandular	**2**	Based on salivary gland volume
Articular	**2**	Correlated with antigen-presenting cell numbers and pro-inflammatory cytokines
Cutaneous	**3**	Correlated with effector T-cell numbers and pro-inflammatory cytokines
Biological	**1**	Correlated with blood total IgG concentration
Constitutional	**3**	Correlated with pro-inflammatory cytokines
Hematological	**2**	Based on lymph node volume

References:

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