Sjögren Syndrome
Why Do Clinical Trials Fail?

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KEYWORDS

- Sjögren syndrome • Benign glandular manifestations
- Extraglandular manifestations • Keratoconjunctivitis sicca • Danger hypothesis
- Danger-associated molecular patterns • Functional circuit
- Neurohypothalamic-immune axis

KEY POINTS

- Failure of benign manifestations, such as fatigue or cognitive impairment, must be shown by current peripheral blood tests.
- Benign symptoms, including dry eye and dry mouth, correlate poorly with objective findings of tear flow and saliva flow.
- Many of Sjögren syndrome patients who have extraglandular manifestations are incorrectly labeled as systemic lupus erythematosus or rheumatoid arthritis patients.

INTRODUCTION

Symptoms of Sjögren syndrome (SS) include both benign and systemic manifestations.

The benign (glandular) symptoms include ocular and oral discomfort. The myalgias and arthralgias, as well as generalized fatigue and cognitive difficulties, are also included in the benign category. However, these features certainly are not benign to the patients.[1–3]

Dry or painful eyes are now the most frequent reason for visits to ophthalmology clinic, and a leading cause of lost work efficiency.

Because patients increasingly sit at computer stations in low-humidity office buildings, tear film dysfunction is exacerbated by the 90% blink rate reduction that accompanies staring at the computer screen.[4]

In the United Kingdom alone, the financial loss from dry eyes alone was estimated at more than £150,000,000.[3,5]

Patients' most commonly identified benign symptom limiting their daily function is the chronic fatigue and loss of ability to function at their previous cognitive level.

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The patients equate this disability at the level of moderate angina, and state that they would be willing to exchange more than 2 years of life expectancy to not have this limitation.[6]

The benign symptoms emphasized here are benign only in their nomenclature; these have been the symptoms that have not shown improvements in clinical trials with biologic agents.[7,8]

Yet, rheumatologists and investigators have assumed that the next anticytokine therapy will have a different and better result than the numerous other anticytokine therapies that are buried in the graveyard of failed clinical trials over the past decade.

The future of therapy for SS is not that bleak but clinicians and investigators must stop and ask about the choice of targets, methods of biomarkers, and trial design.

- If extraglandular manifestations of SS are going to be targeted, suitable SS patients must be identified and more efficiently enrolled. This involves education of rheumatologists and other specialists about sick SS patients misclassified as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) patients.
- If benign symptoms are going to be targeted, neurochemists have much to teach about the pathways that mediate these symptoms. A broader understanding of the innate immune system and how it interacts with the central immune system is provided by murine sickness models after viral infection.

BACKGROUND

To consider the future of therapy in SS, the concept of the danger hypothesis that gave rise to exploration of the innate immune system and its interactions with the central nervous system (CNS) is reviewed (**Box 1**).[9–14]

This hypothesis includes the traditional adaptive or acquired immune system of T-cell–mediated B-cell production of autoantibodies. However, it also includes the interactions of the innate immune system with elements of the CNS.

The adaptive (or acquired) immune system is based on Medewar's failure of tolerance model, and has provided a family of drugs used to treat the extraglandular manifestations of SS, including disease-modifying antirheumatic drugs (DMARDs) and many biologic drugs.

However, it was recognized more than 25 years ago that the adaptive peripheral immune system did not adequately explain the interaction of the peripheral immune system with the CNS. A broader immune system was proposed to distinguish self from exogenous infections, as outlined by the danger model hypothesis of Gallucci and Matzinger[10] and Janeway and Medzhitov[12,14] (see **Box 1**).

In the danger model, the peripheral innate immune system still provides the first line of defense but subsequently interacts with the midbrain, the cerebral cortex, and the hypothalamic-adrenal axis by a series of danger-associated molecular patterns (DAMPs) leading to up regulation of toll-like receptors (TLRs) in activated astroglial cells. This activation results in up regulation of neurohormones, cytokines, neurokines, prostaglandins, and neurotransmitters. Morris and colleagues[15] have recently summarized the interactions between activation of DAMPs and central mechanisms of fatigue that involve pathways of tumor necrosis factor (TNF), interferon (IFN)-1 and -2, and ultimately mitochondrial processing of ATP. This is shown schematically in **Fig. 1**.[15]

REASONS FOR FAILURE OF TRIALS OF BIOLOGICS IN SJÖGREN SYNDROME TRIALS

It is important to point out that there has not been total failure of biologics in SS. Reasonable results in the control of extraglandular manifestations of SS have been achieved.