

Disease activity in primary Sjögren's syndrome – can it be defined and assessed?

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Primary Sjögren's syndrome (pSS) is a chronic rheumatic disorder characterised by autoimmunological, immunoinflammatory and lymphoproliferative activities universally affecting exocrine organs and resulting in structural damage and functional defects. Additional involvement of nonexocrine tissues occurs frequently, but general malaise symptoms due to the lymphocytic activities are rare.

Curative treatments for pSS are not available due to incomplete insight into the etiopathogenic factors. Also, the clinical evidence, which should recommend disease-modifying therapy, is still too sparse and empirical to allow an exact and evidence-based algorithm for therapeutic decision-making. Improved drug therapy recommendations for pSS should be based on a detailed assessment of disease status (activity and damage) and directed towards clinically meaningful endpoints. Unfortunately, there are neither "golden standards" nor any expert consensus regarding measures of disease status or outcome in pSS. This paper is aimed to highlight present means to estimate disease activity in pSS.

Disease activity is a clinical notion which refers to the fundamental disease processes and implies features of both pathogenesis and organ reactions. Conceptually, disease activity is reversible as opposed to organ damage being irreversible and caused by longstanding activity. In the vast majority of patients disease activity is reflected by clinical symptoms and signs, however, silent or subclinical activity can be traced in asymptomatic individuals by using sensitive laboratory and physiological tests. Remission is defined as a state of spontaneous or drug-induced suppression of disease activity to a stable level where symptoms are at a minimum. For some disorders disease activity is a simple and well-defined phenomenon, e.g. in polymyalgia rheumatica, whereas in other cases, e.g. SLE and primary vasculitides it is a complex condition composed of coexisting disease processes located to different organs or tissues. In order to define and operate with disease activity it is, therefore, essential to pin point the fundamental disease processes underlying the clinical manifestations.

In pSS disease activity most likely is a complex phenomenon involving co-operating features of the fundamental etiopathogenic processes and of the organ reactions. There is neither a "gold standard" nor any published expert consensus regarding activity measures for the disease. Also, it is unknown if disease activity changes qualitatively from early to long-standing disease. A key feature of disease activity is whether or not it leads to organ damage. If so, markers of disease activity should be elaborated from examination of patient materials, including cases with progressive organ damage. This would require follow-up studies from disease onset to chronicity. However, no such studies have been reported, which is easily understood in view of the usual time gap between onset of symptoms and establishment of diagnosis.

From studies of patients with long-standing pSS we find evidence that the immunopathological processes proceed at a constant or slowly increasing rate parallel to unchanged or slowly deteriorating clinical (exocrine) status. To explain this, it is necessary to understand the means by which clinical manifestations are examined. Thus, it is likely, that most of the routinely used clinical and pathophysiological tests measure both activity and damage. As an example, reduced pulmonary diffusion capacity may result from (potentially) reversible interstitial lymphocytic inflammation, as well as from irreversible pulmonary fibrosis. Also, low glandular secretion rate may reflect the reversible influence of immune cell activities, as well as irreversible parenchymal loss. Deteriorated clinical status will, therefore, not necessarily mean further damage, and unaltered status could veil decreased activity along with increased damage. If disease activity in pSS always leads to damage,

then the hitherto examined immunopathological markers appear not to represent the bottom line of pathogenesis. Alternatively, disease activity may continue without significant progression of organ damage.

As formerly mentioned disease activity implies reversibility, a feature that does not really characterise the reported spontaneous courses of pathogenetic and clinical disease measures. Tools to monitor disease activity more likely can be deduced from treatment studies aimed at decreasing the abnormal immune cell activities. Table 1 shows results from reported clinical trials in which key markers of surface exocrine disease and of the immunopathogenesis of Sjögren's syndrome have been the subjects for follow-up examination. The data suggest that immunomodulating/anti-inflammatory treatment is able to down-regulate B-lymphocyte activity and diminish lymphocytic inflammation in minor salivary glands, but in most studies without improving the objective clinical status. In contrast, trials with bromhexine (10) and essential fatty acids (11) have demonstrated significant reversibility in the markers of ocular exocrine disease suggesting that in these cases not only damage is being measured. Three recent large-scale clinical trials in Sjögren's syndrome have provided new insight into the relation between activity and damage underlying hyposalivation of lacrimal and salivary glands. In two independent studies administration of oral pilocarpine (13, 15), a parasympathomimetic drug, improved tear and whole saliva flow rates as compared to placebo. Shiazowa et al. (14) treated 60 Sjögren's syndrome patients with oral interferon alpha or placebo for 6 months and reported increased saliva output in the actively treated group, moreover, follow-up minor salivary gland biopsies performed selectively on interferon alpha responders showed a reduction in the extent of chronic focal sialadenitis. The improvements shown in the pilocarpine studies most probably reflect the capacity of residual exocrine tissue to respond to a pharmacological stimulus whereas the interferon alpha study indicates a possible disease-modifying role of cytokine therapy in pSS. In summary, these randomised placebo-controlled clinical trials suggest that, in at least some patients, hypofunction of exocrine glands as well as chronic focal sialadenitis are in part reversible disease manifestations and thus reflect both activity and damage.

In conclusion, the clinical means to assess disease manifestations appear unsuited for selectively measuring disease activity. Moreover, there is no present evidence to suggest that disease activity in pSS can be accurately estimated by measuring only one or a few B or T lymphocyte products (ref). Clinically useful markers of pathogenesis should, therefore, be unveiled from examination of a broad spectrum of measures, reflecting both the autoimmune, lymphoproliferative and immunoinflammatory aspects of the disease processes. For that purpose, it is interesting to note that the list of measurable immune activation products in pSS patients is steadily expanding, including additional autoantibodies (16), cytokines (17) and solubilised lymphocyte membrane molecules (18).

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Table. Combined assessment of disease activity and outcome measures as reported in clinical trials on Sjögren's syndrome

Drug	Dose	Study design	Number of patients	Treatment period (mo)	Treatment-related changes in activity and outcome			Ig. Ref. No.	
					Clinical measures		Pathogenetic measures		
					Ocular	Oral	Lympho. infl.		Autoab.
Prednisolone	40mg/2 days	No controls	7	6	Sch. RB	LSG	1		
Prednisolone	30mg/2 days	Placebo group	8	6	Sch. RB	LSG	2		
Hydroxy-chloroquine	200mg/day	Control group	10	12	Sch.	LSG	3		
Hydroxy-chloroquine	400mg/day	Placebo cross-over	19	12	Sch. RB BUT	Galliumscan.	4		
Hydroxy-chloroquine	6-7mg/kg/day	No controls	40	>24	Sch. RB	LSG	5		
Cyclosporine	5mg/kg/day	Placebo group	7	6	Sch.	LSG	6		
Cyclosporine	5mg/kg/day	Placebo group	10	6	Sch.	LSG	7		
Nandrolone decanoate	100mg/14 day	Placebo group	10	6	Sch. RB	LSG	8		
Methotrexate	0.2mg/kg/week	No controls	17	12	Sch. RB BUT	LSG	9		
Pilocarpine	10-20mg/day	Placebo group	373	3	Glob.	LSG	13		
Pilocarpine	20-30mg/day	Placebo group	256	3	Glob.	LSG	15		
Interferon-	450/mg/day	IFN- vs. Sucralfate	60	6	Sch. RB	LSG	14		
Azathioprine	1mg/kg/day	Placebo group	25	6	Sch.	LSG	12		
Bromhexine	48mg/day	Placebo cross-over	32	3 weeks	Sch. BUT RB	LSG	10		
Essential fatty acids	3g/day	Placebo cross-over	28	2	Sch. BUT RB	LSG	11		

Lympho. infl.: degree of lymphocytic infiltration in minor salivary glands; Autoab.: serum autoantibody level; Ig.: plasma immunoglobulin level; Ref. No.: reference number
 Sch.: Schirmer-I-test; RB: Rose Bengal Score; BUT: Break-up Time; Sal. flow: saliva flow rate; Glob.: global disease assessment; LSG: labial salivary gland biopsy
 : significant improvement=change towards normality; : unchanged