Sjogren's Syndrome Update

Michigan Rheumatism Society

Mackinac Island

10.01.2021

Elena Schiopu, MD

Goals

- Sjogren's Syndrome: semantics of primary and secondary SjS
- 2017 ACR/EULAR Classification Criteria
- Updates on SjS-specific antibodies
- Early assessment of organ involvement
- Patient reported outcomes
- Longitudinal assessment of organ damage
- Treatment strategies
- Future directions

A bit of history…

- 1888, the surgeon Dr. Johann Mikulicz reported to the Society for Scientific Medicine in Koenigsberg the case of a 42-year-old farmer presenting with painless bilateral swelling of the lacrimal and salivary glands. After complete surgical excision of the lacrimal glands, as well as both submaxillary glands, the patient seemed to feel better; died of peritonitis
- Dr. Henrik Sjögren (1899–1986), born near Stockholm
- Studied at the Karolinska Institute in Stockholm
- Graduated as a medical doctor in 1927
- 1933: 19 patient case series of “sicca syndrome”, 13 of which had arthritis
- Wife Maria (also an ophthalmologist) helped collect patients
- Rose Bengal (tetraiodo-tetrachlor-fluorescein) and Schirmer’s test
- At 77: honorary member of the Swedish Rheumatological Society and attended the First International Symposium on Sjögren’s Syndrome

Sjogren Syndrome (SjS)

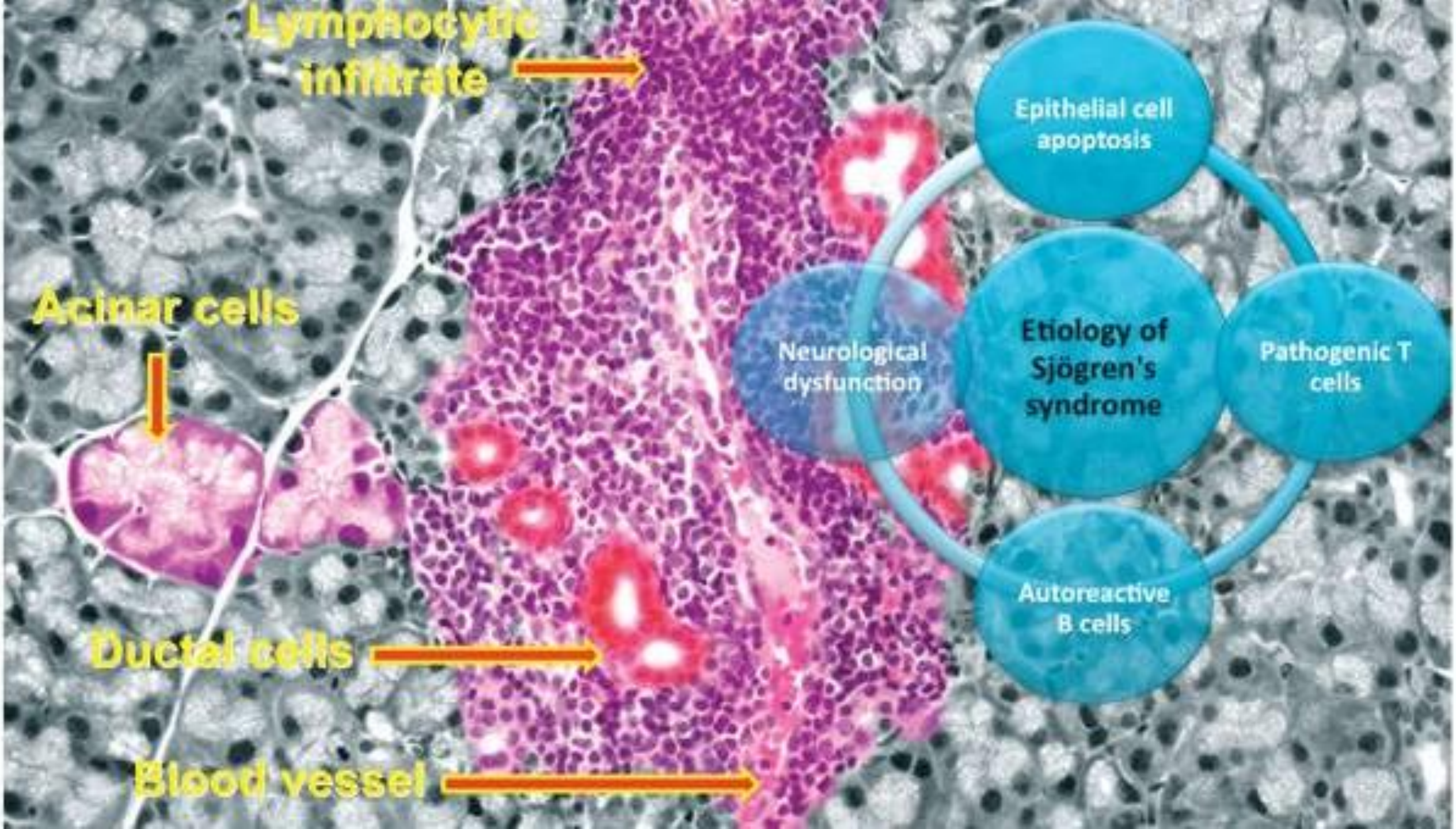
- Sjögren's syndrome, a chronic process, is among the most commonly occurring rheumatologic diseases (0.3-1/K); 1:9 male: female. Avg age 50. Secondary SjS: SLE, SSc, RA, IIM
- The clinical hallmark of this disease (80%):
  - exocrinopathy (dry eyes and mouth)
  - MSK pain
  - fatigue
- The disease often extends beyond the exocrine glands to seriously affect other organs systems (30-40%): esophagus, lungs, kidneys, muscle, joints, and nervous system (CNS/PNS)
- Patients with primary Sjögren's syndrome develop MALT/non-Hodgkin's B cell lymphoma at a substantially higher rate than the general population (by a factor of 15-20)

Mariette et al N Engl J Med 2018;378:931-9

Language Matters: “primary” vs. “secondary”→SjS Associated With

- Blurry lines distinguishing between primary and secondar
- “secondary” then less researched, often excluded form clinical trials, undertreated
- 30% of SjS are associated with POLYAUTOIMMUNITY: SLE, RA, SSc
- Historically the term ‘secondary’ SjS arose from a concept of chronically ‘pre’-activated lymphocytes causing non-specific and antigen-independent infiltration of the salivary and lacrimal glands, which were thought to be prone for a breach in immune tolerance
  - SjS alone: parotitis, Raynaud’s phenomenon (RP), purpura, lymphadenopathy, myositis and renal involvement
  - SjS/RA: interstitial lung disease and arthritis; worse Sharp score compared to RA alone
  - SjS/SLE: higher prevalence of RP, arthritis and central nervous system involvement, and a lower frequency of lymphadenopathy; perhaps milder SLE
  - SjS/SSc: similar phenotypes; perhaps milder SSc

F Kollert et al, Rheumatology 2020;59:1218–1225


Lymphocytic infiltrate
Acinar cells
Ductal cells
Blood vessel
Epithelial cell apoptosis
Neurological dysfunction
Etiology of Sjögren's syndrome
Pathogenic T cells
Autoreactive B cells

Pathophysiology of pSS

- activation of mucosal epithelial cells from viral stimulation? or from abnormal production of endogenous viral elements.
- Activation of innate + adaptive immune system → autoantibody production
- Type I and II IFN are present in the salivary glands: viral agents?
- Genome wide studies linked SjS to IFN genes
- Presence of germinal centers in the salivary glands → B-cell activation
- Presence of plasmablasts in the blood; plasma cells in the salivary glands and of activated CD8 T cells in the blood and glands
- B-cell activating factor of the tumor necrosis factor family (BAFF), a cytokine that promotes B-cell maturation, proliferation, and survival, is increased in primary Sjögren's syndrome; BAFF is induced by type I&II IFN

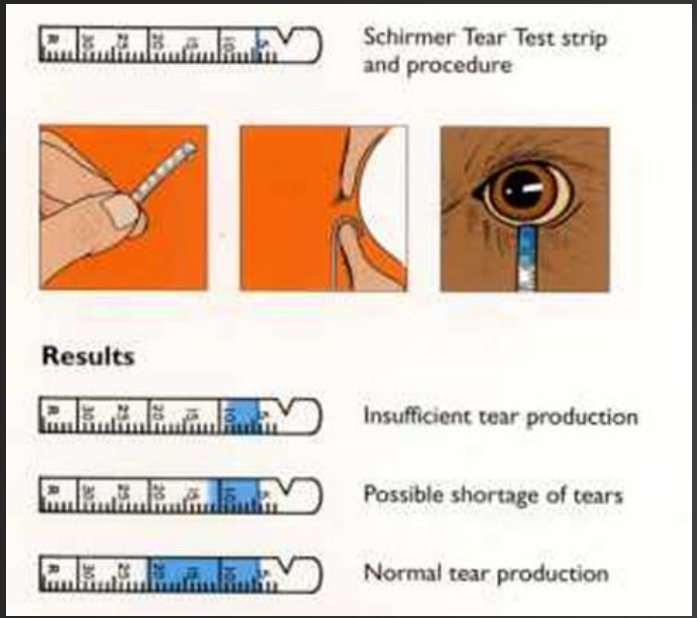
Table 1. 2017 ACR–EULAR Classification Criteria for Primary Sjögren's Syndrome.*

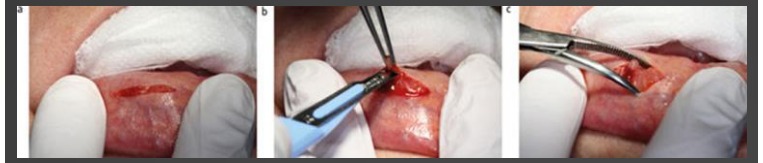
Item	Description	Score
Focus score of ≥1	A score determined by the number of mononuclear-cell infiltrates containing ≥50 inflammatory cells per 4 mm^2 of minor labial salivary gland obtained on biopsy	3
Presence of anti-SSA antibodies†	Measured in serum; only anti-Ro60 antibodies have to be considered; isolated anti-Ro52 antibodies are not specific for Sjögren's syndrome	3
SICCA ocular staining score of ≥5	A score determined by an ophthalmologist on the basis of examination with fluorescein and lissamine green staining; scores range from 0 to 12, with higher scores indicating greater severity	1
Schirmer test of ≤5 mm per 5 min	An assay for measuring tear production by inserting filter paper on conjunctiva in the lower eyelid and assessing the amount of moisture on the paper	1
Unstimulated whole salivary flow of ≤0.1 ml per min	An assay for measuring the rate of salivary flow by collecting saliva in a tube for at least 5 min after the patient has swallowed	1
Total score		**9**

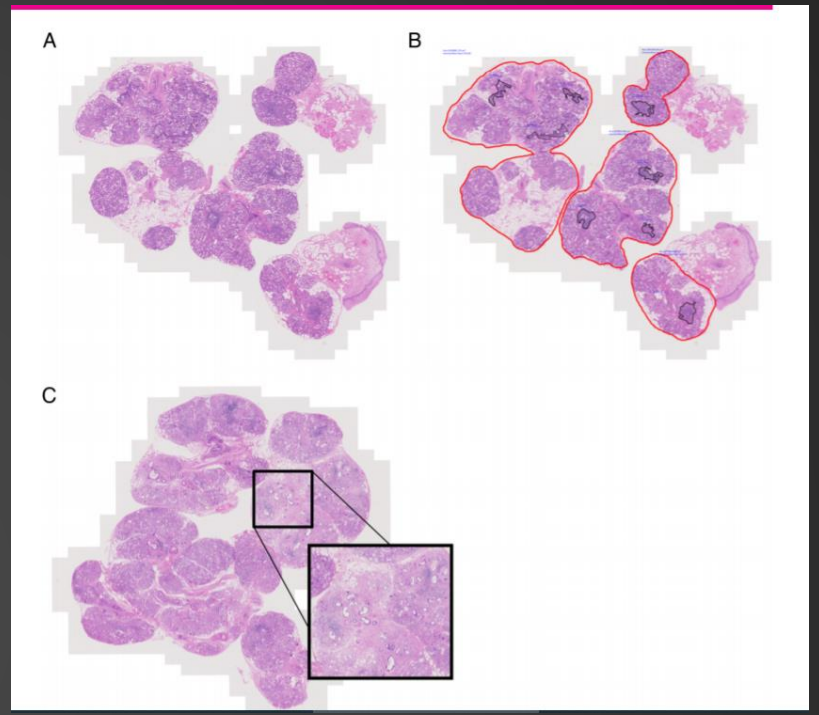
* On the basis of the listed classification criteria, a diagnosis of primary Sjögren's syndrome is defined as a score of 4 or more. These criteria apply to patients who have at least one symptom of ocular or oral dryness or the presence of systemic manifestations suggestive of primary Sjögren's syndrome. Exclusion criteria include active hepatitis C virus infection on polymerase-chain-reaction assay, radiotherapy of the cervical spine, sarcoidosis, graft-versus-host disease, receipt of anticholinergic drugs, and IgG4-related disease. ACR denotes American College of Rheumatology, EULAR European League against Rheumatism, SICCA Sjögren's International Collaborative Clinical Alliance, and SSA anti–Sjögren's syndrome–related antigen A.

† Positive serologic results for anti-SSB/La antibodies in the absence of anti-SSA/Ro antibodies is not specific and is no longer considered to be a criterion for the diagnosis.

Shiboski CH, et al. Ann Rheum Dis 2017;76:9–16. doi:10.1136/annrheumdis-2016-210571





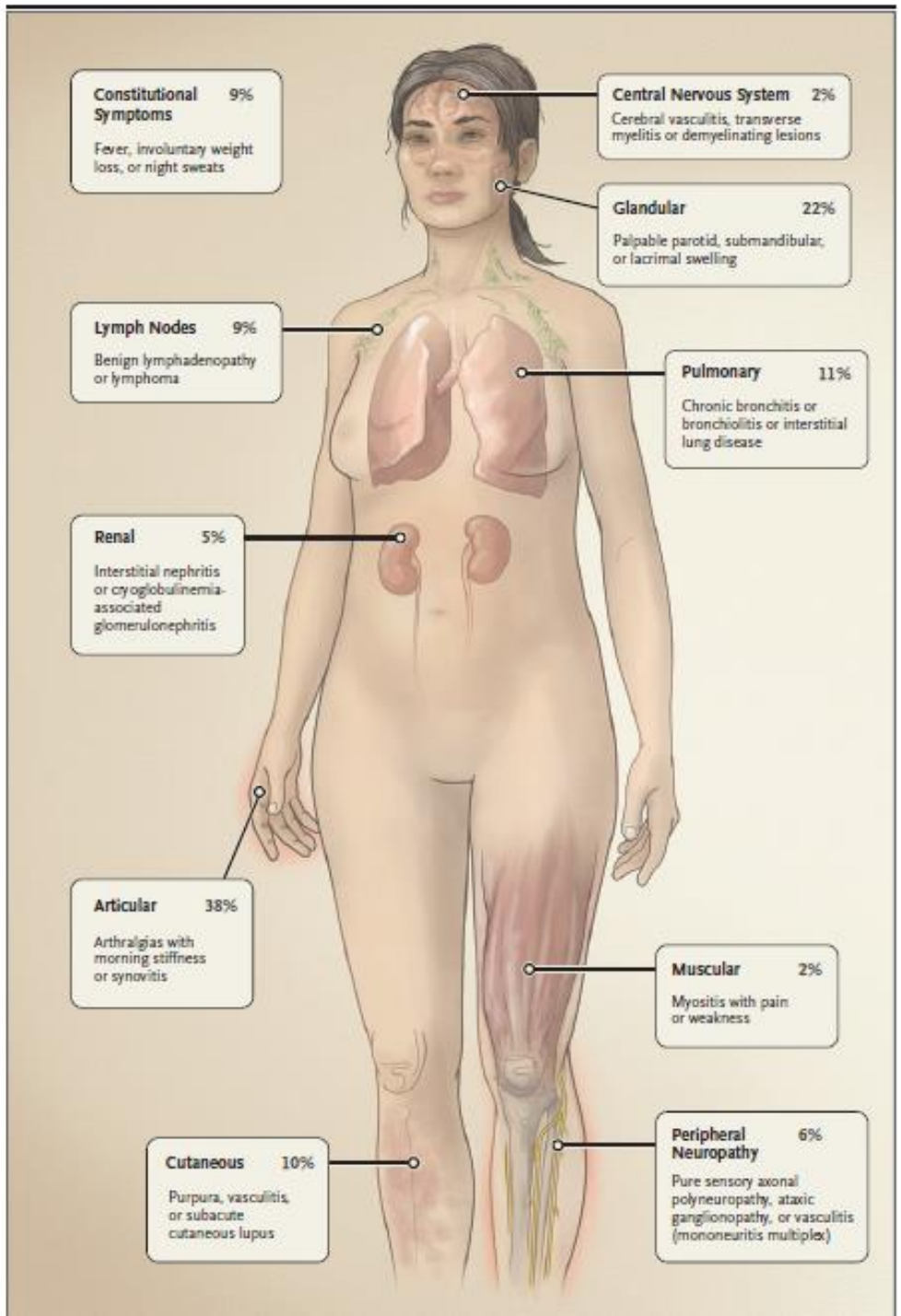


A: H&E stain of salivary gland biopsy

B: delineation of glandular tissue in red;

FOCUS score: calculated by counting the number of foci, whose area is delineated within the black lines, dividing by the whole glandular surface area in mm2 and multiplying by 4 to give the number of foci per 4 mm2 over the whole glandular area

Fisher BA, et al. Ann Rheum Dis 2016;0:1–8. doi:10.1136



Clinical Manifestations of SjS

- Dryness in mouth, eyes, vaginal, skin
- Fatigue, sweats, weight loss
- Organ specific symptoms/signs
  - Glandular/Parotid gland enlargement
  - GI: upper esophageal dysmotility, constipation
  - Arthralgia/arthritis: nonerosive
  - Rash-purpura-vasculitis-SCLE
  - CNS, PNS
  - ILD: LIP, NSIP
  - Cytopenia
  - Interstitial nephritis
  - Myositis
  - Lymphoma(MALT)

Initial Suggested SjS Evaluation

- Great PE:
  - HEENT: inspect for parotid enlargement, feel SGD; check for LAD; periorbital tissue; dentition
  - Lungs/heart: listen for end-inspiratory rales; search for P2, parasternal heave
  - MSK: attention to synovitis; MMT8
  - Skin: LCV, cryo, check for ulcerations
- Labs: CBC, CMP, CK/aldolase, ANA, ENA, RNA pol III, myomarker 3 (SSA 52kDa, U1-RNP, Pm/Scl), BNP, SUA, UPEP/SPEP, IgG/A/M levels, IgG subtypes, U/A, U Pr/Cr ratio, C3, C4, ANCA/MPO/PR3, histo/fungal, Hep B/C, HIV, RF/CCP, ESR/CRP, Quantiferon, D, Mg
- Xrays: hands, feet, pelvis (SIJ)
- CXR: mediastinal LAD, gross ILD, thymic tissue
- Echocardiogram (mention PAH in the requisition), PFT, HRCT, hallwalk?, VFSS/esophagram
- **Salivary gland involvement:**
  - Histopathology: minor salivary gland biopsy
  - Sialography/Scan/US/MR/Sialometry
- **Lacrimal gland involvement**
  - Shirmer test
  - Occular staining

Exclude Other Causes of Sicca

- HCV
- HIV
- Sarcoidosis
- Hyper IgG4
- s/p neck radiation
- GVH
- Drugs: diuretics, antihistamines, TCA, neuroleptics

FMS

UMHS: Department of Rheumatology: Patient Questionnaire

1. For each symptom listed below, use the following scale to indicate the severity of the symptom **during the past 7 days.**

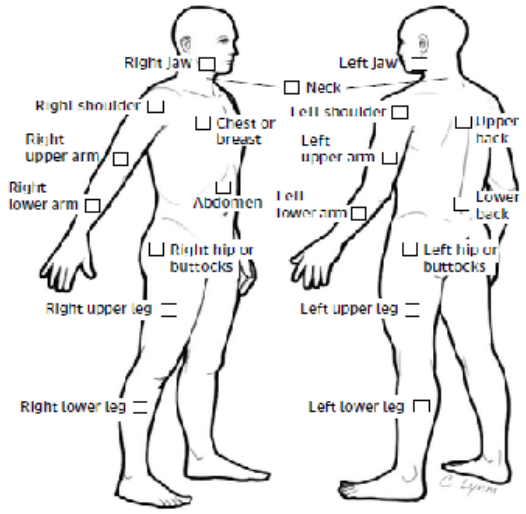
	No Problem	Mild (Mild/Intermittent)	Moderate (Considerable /often present)	Severe (Continuous/life disturbing)
Fatigue	☐	☐	☐	☐
Trouble thinking or remembering	☐	☐	☐	☐
Waking up tired (unrefreshed)	☐	☐	☐	☐

2. Indicate which of the following symptoms you have had over the past 7 days by circling the symptom:

Bladder spasms	Easy bruising	Insomnia	Numbness/tingling
Blurred vision	Fatigue	Irritable bowel syndrome	Oral ulcers
Chest pain	Fever	Itching	Pain in upper abdomen
Constipation	Frequent urination	Loss of appetite	Pain/cramps in abdomen
Depression	Hair loss	Loss/Change in taste	Painful urination
Diarrhea	Headache	Muscle pain	Rash
Dizziness	Hearing problem	Muscle weakness	Raynaud phenomenon
Dry eyes	Heart burn	Nausea	Hives
Dry mouth	Seizure	Shortness of breath	Sun sensitivity
Vomiting	Wheezing	Ringing in ears	Thinking/memory problem
Nervousness			

3. Have the symptoms in 1-2 been present at a similar level for at least **3 months**? Yes ☐ No ☐

4. On the image below, **CHECK ALL** areas of your body where you have had pain or tenderness which has **persisted or recurred** for **the last 3 months or longer**.



5. If you have had **NO PAIN** please check this box: ☐

6. If you marked pain, do you have a disorder that would otherwise explain the pain? If so what disorder?
Yes ☐ ———————
(list the disorder)
No ☐

Adapted from Clauw DJ. Fibromyalgia: A Clinical Review. JAMA. 2014;311(15):1547-1555. doi:10.1001/jama.2014.3266

- Widespread pain index (WPI): 0-19
- Symptom Severity scale (SS): 0-12
- Sensitive to change
- YES FMS if;
  - WPI ≥ 7 & SS score ≥ 5
  - WPI 3-6 & SS score ≥ 9

Wolfe et al. Arthritis Care & Res, oct 1, 2010

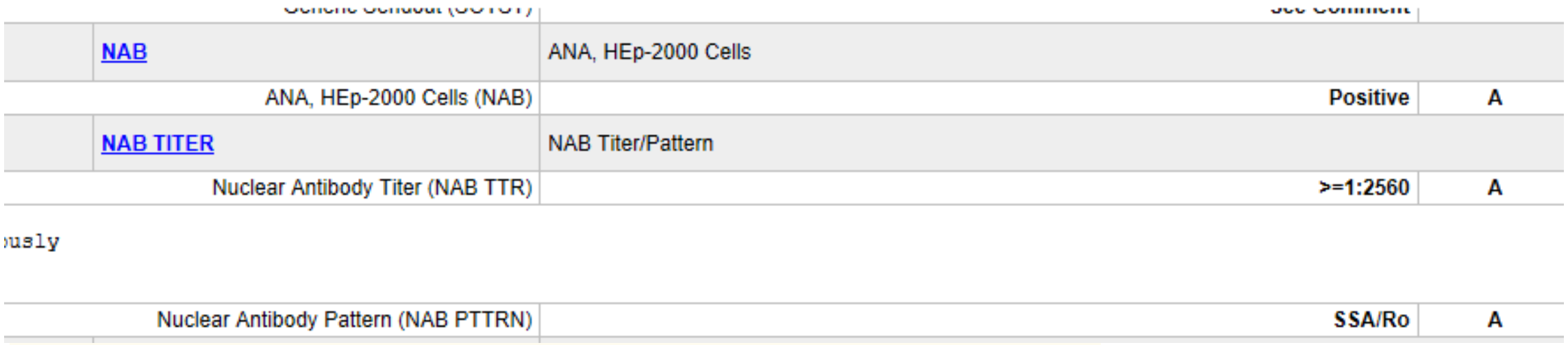
SjS antibodies

- Present 18-20 y before classifiable disease (like SLE, RA)

Commonly described autoantibodies in Sjögren's syndrome.

Autoantibodies	Prevalence	Properties	Clinical Association
ACA	3–27%	subphenotype marker	Raynaud's phenomenon
Anti-M3R	60–80%	potential pathogenic role	sicca

- salivary gland protein 1 (SP-1)
- carbonic anhydrase 6 (CA6)
- parotid secretory protein (PSP)



	NAB	ANA, HEp-2000 Cells	
ANA, HEp-2000 Cells (NAB)		Positive	A
	NAB TITER	NAB Titer/Pattern	
Nuclear Antibody Titer (NAB TTR)		>=1:2560	A
Nuclear Antibody Pattern (NAB PTTRN)		SSA/Ro	A

Fayyaz et al Rheum Dis Clin North Am. 2016 Aug; 42(3): 419–434.

Serologies Anti-Ro/SSA Ab

- Ab against Ro/SSA autoantigens recognizing two cellular proteins:
  - Ro60 or 60kDa localized in nucleus or nucleolus (TROVE2)
    - Binds to RNA. Role in regulation of mRNA, hasten degradation of defective RNA, bind to cellular and viral RNA,
  - Ro52 or 52kDa localized in the cytoplasm (TRIM21)
    - Interferon inducible protein, E3 ubiquitin ligase- adding ubiquitin molecules to target proteins potentially enhancing degradation of proteasomes, may regulate mRNA, down regulates NFkB(inhibits kinase), inhibits Interferon Regulatory Factors (IRF)
  - Most commercial labs use a single test ”Anti Ro” for both antibodies using combination of both antigens
- Most frequently seen in pSS(Ro60 -67% and Ro52-75%) and SLE(Ro60-49% and Ro52-43%)
  - but also in PM, DM, SSc, MCTD, PBC, rapidly progressive ILD
- May be the only positive Ab in >50% of “ANA negative SLE”
- Ro 52 kDa is an “independent contractor”: not predictive of AIDs lone, but often found in association with SLE-, SSc-, IIM-, RA- specific antibodies; rapidly progressive ILD
- Commonly present in pts with Subacute Cutaneous Lupus
- Detectable in pts with SLE years or decades before dx of SLE

Anti SSB/La Ab

- Ab against La/SSb autoantigens recognizing 47 kd cellular proteins:
  - 47kd localized in nucleus, also shuttles between nucleus and cytoplasm
    - Participates in processing of non coding RNA- (r) RNA, binds (t) RNA, viral RNA(translation of viral RNA), potential regulation of m(RNA) stability and translation

- Specific Ab for SLE and pSjS
- May be detected in mothers of children with neonatal lupus syndrome

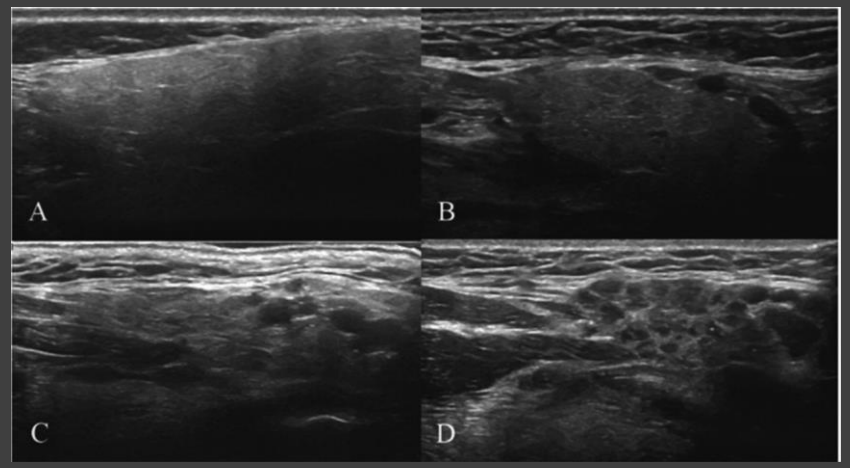
Autoantibodies to Cytosolic 5′-Nucleotidase 1A (cN-1A; NT5C1A)

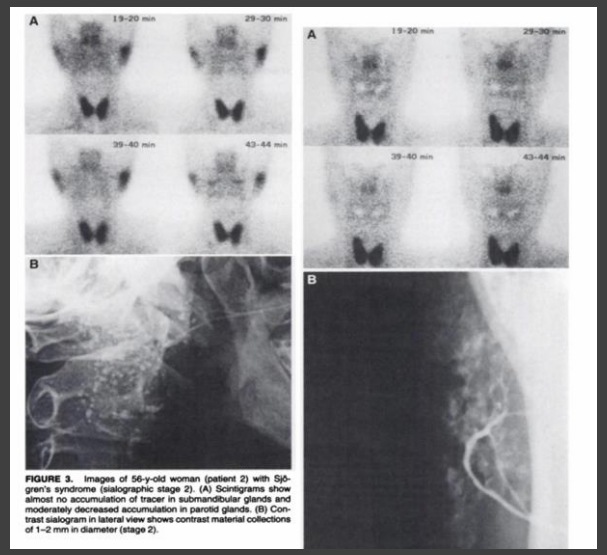
- cN-1A: enzyme involved in the conversion of adenosine monophosphate → adenosine; role in the dephosphorylation of nucleotides to nucleosides
- 2013: 2 independent groups found it specific to IBM (33–76% of IBM)
- Sera from pSS (n = 193) and SLE patients (n = 252), 5 European centers, using ELISA (Euroimmun AG) in a single laboratory:
  - 12% of pSS patients (range: 7–19%)
  - 10% of SLE patietns (range: 6–21%)
  - No relationship w presence/absence of: anti-Ro52, anti-nucleosome, and anti-dsDNA in both pSS and SLE
  - No relationship w frequency of muscular symptoms or viral infections
  - + anti-cN-1A patients had more “other AID”

Rietveld et al Front Immunol. 2018; 9: 1200 doi: 10.3389/fimmu.2018.01200

Assessing Salivary Glands and Lacrimal Glands in SjS

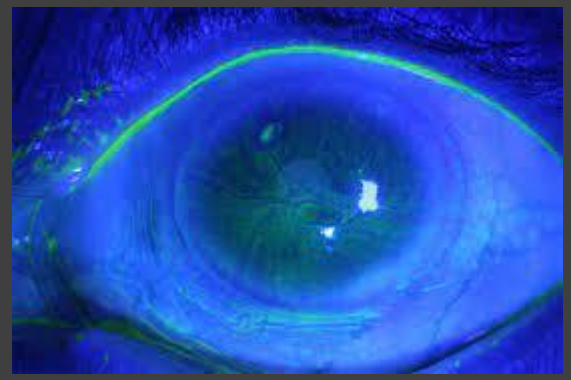
- Imaging of Salivary glands:
  - US
  - Sialography
  - Scintigraphy
  - MR





Assessment of Lacrimal Glands:

- Schirmer test
- Fluorescein ocular staining (ophthalmologist)



GI Involvement in SjS

- Esophageal dysmotility in 41% of a small series, mostly upper 1/3; no relationship with parotid gland function, antibodies, other SjS manifestations; easily overlooked in the setting of oral sicca
- Chronic inflammatory pancreatitis, and hepatitis
- 67% have GERD

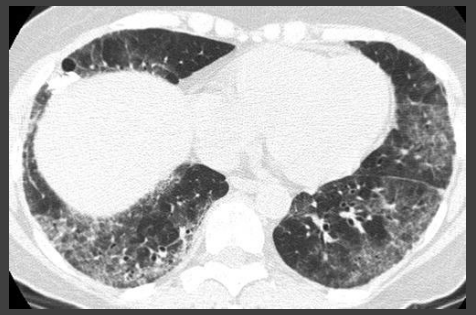
Consider obtaining a detailed dysphagia history (early/late swallow, etc) and a functional esophageal study at baseline and as needed later:

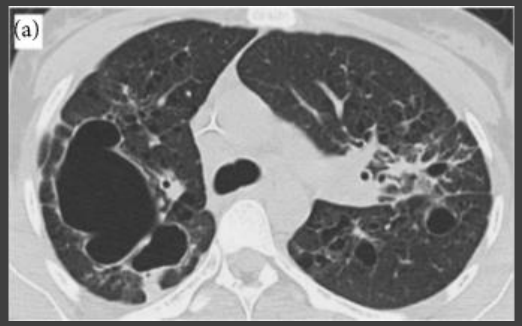
- VFSS
- Esophageal manometry/pH-metry
- esophagram

Tsianos et al Scand J Rheumatol Suppl 1986;61:151-5
Volter et al Dig Dis Sci 2004 Feb;49(2):248-53

Lung Involvement in SjS

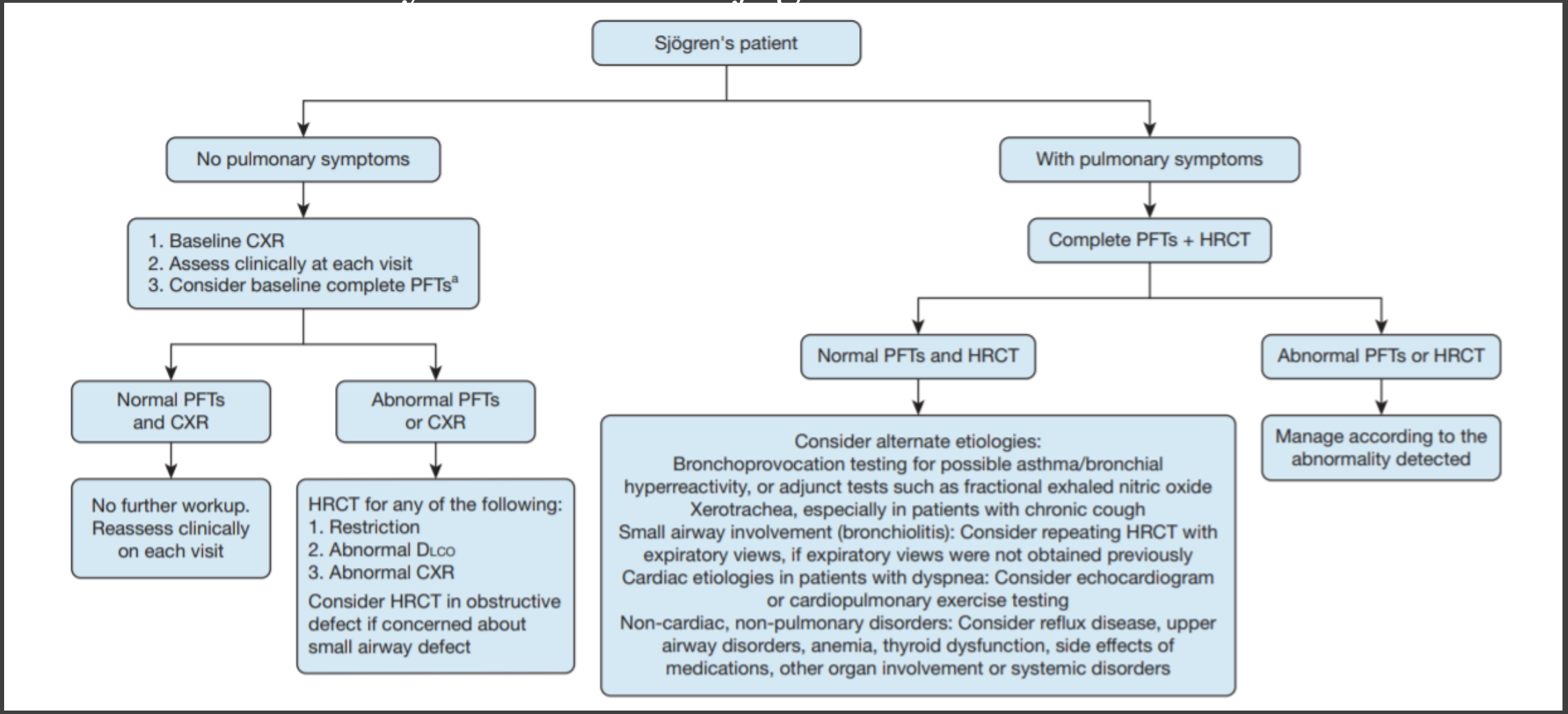
- Most prevalent extra-glandular manifestation (9-75%) depending on methods
- Initial symptoms: cough, DOE, effort intolerance
- HRCT: ground-glass attenuation, thin-walled cysts, honeycombing, reticular pattern, small nodules and enlarged mediastinal lymph node
- PFTs: restrictive picture ↓FVC, ↓Dlco
- Swedish series: 22% prevalence, poor survival
- Most common: NSIP
- Most specific: LIP





Palm et al, Rheumatology, Volume 52, Issue 1, January 2013, Pages 173–179

Consensus Guidelines for Evaluation and Management of Pulmonary Disease in Sjogren's

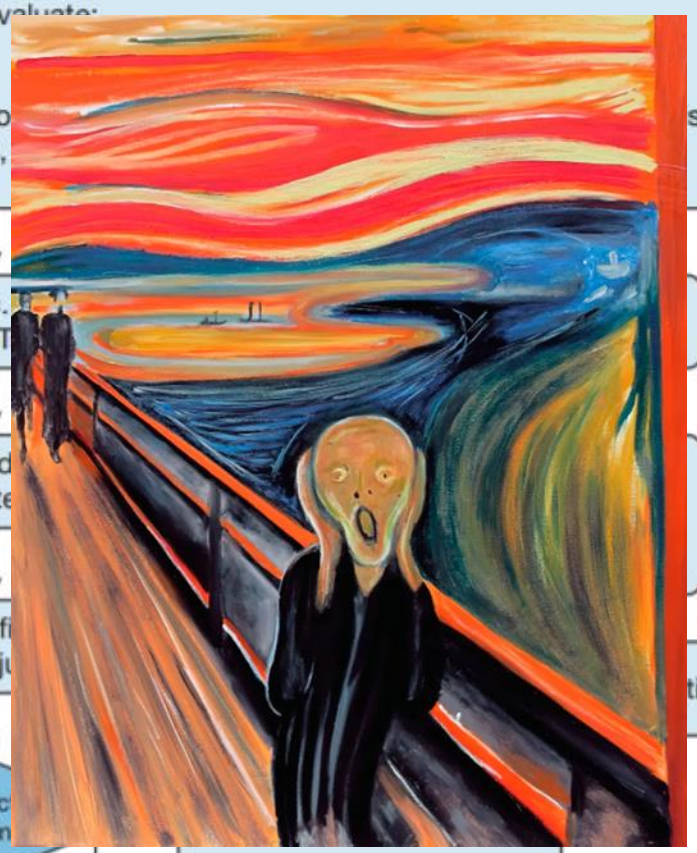


Lee et al CHEST 2021; 159(2):683-698

Patient with Sjögren's-ILD

Evaluate:
1. Functional capacity
2. Pulse oximetry at rest and with activity
3. Critical review of HRCT with thoracic radiolo
4. Close monitoring of PFTs every 3-6 months,
5. Consider echocardiogram if suspected PH

scussion



No or minimal symptoms
Mild PFTs/HRCT

Serial observation off therapy

Symptomatic.
severe PFT

Moderate d
corticoste

MMF or AZA as f
sparing or adj

Satisfac
respon

Yes

Continue MMF or AZA.
Taper steroids to off or lowest most effective dose[b]

No

Critical review of HRCT to determine primary pattern – fibrotic versus inflammatory

Inflammatory

tic drug[d]

Try RTX or calcineurin inhibitors[e] or CYP

Continue close serial monitoring

Satisfactory response

Yes

Continue course

No

Reassess for alternative diagnosis or comorbid conditions. Consider palliative care, lung transplant

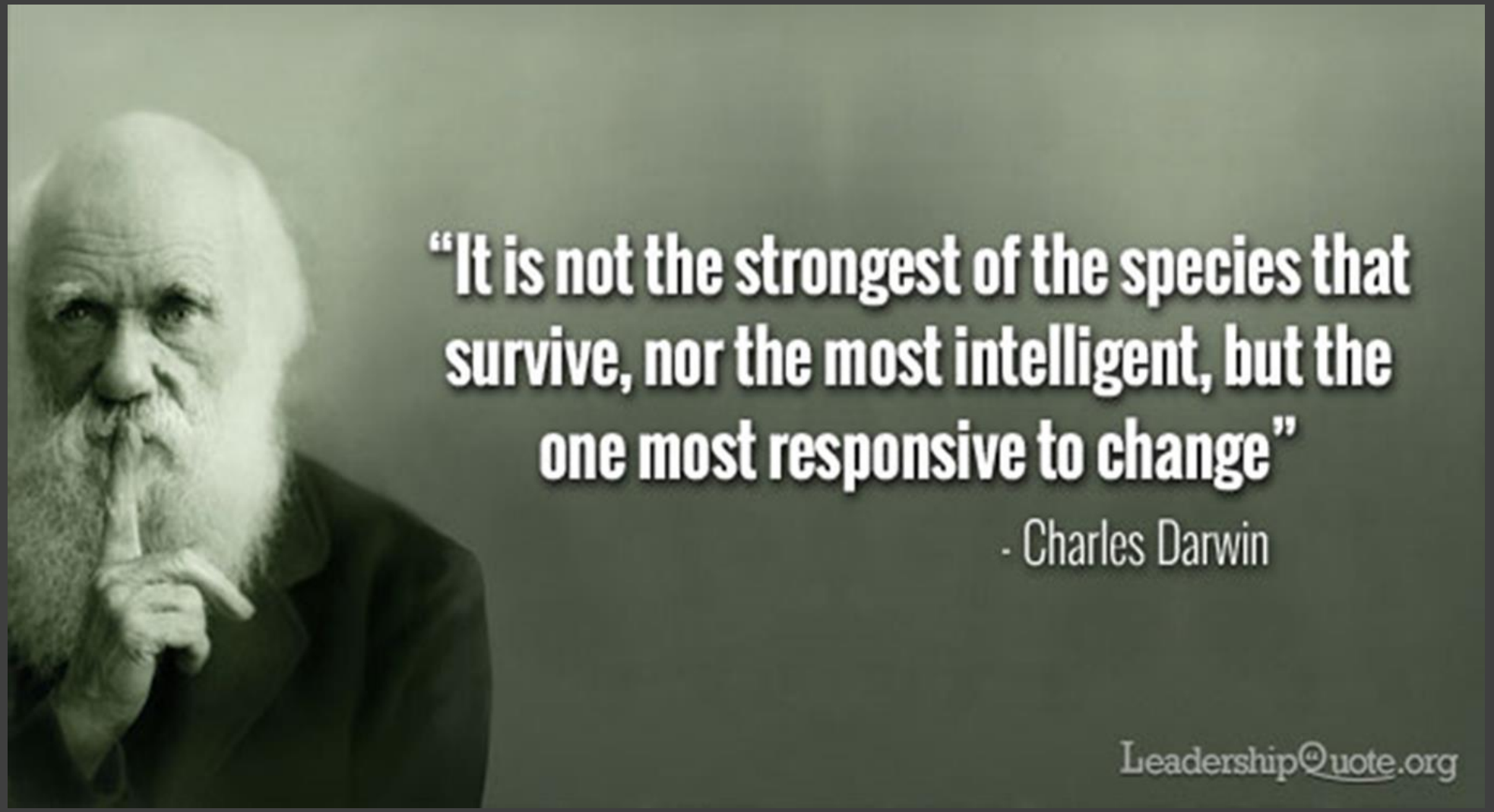
PAH in SjS (Again, DEI)

- Traditional knowledge that there is no PAH in SjS
- However:
  - +Ro: more RP, more "cardiac"
  - SjS is a glandular epithelitis; vasculitis, ILD common
  - Personal observation: 1:5 of my SjS had PAH
- Turkish 43-patients series using RVSP $\geq$ 30 mmHg by Echo doppler: 11 (23.4%)
- China series published in 2020:
  - 103 patients with pSS-PAH; 526 pSS-non-PAH
  - anti-SSB ($p<0.001$, OR 4.095), anti-U1RNP antibodies ($p<0.001$, OR 29.518), age of pSS onset ($p<0.001$, OR 0.651) and the positivity of corneal staining ($p=0.003$, OR 0.409) = independent risk factors
  - 1-, 3- and 5-year survival rates were 94.0%, 88.8% and 79.0%

Kobak et al, Autoimmune Dis Vol 2014, Article ID 710401, 5 pages
Wang et al, Eur Resp J 2020 56: 1902157 DOI: 10.1183/13993003.02157-2019

EULAR Sjögren’s Syndrome (SS) Disease Activity Index (ESSDAI)

EULAR Sjögren’s syndrome (SS) Patient Reported Index (ESSPRI)


"It is not the strongest of the species that survive, nor the most intelligent, but the one most responsive to change"
- Charles Darwin
LeadershipQuote.org

ESSPRI (0-10, MCID 1)

The EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI)

1. How severe has your **dryness** been during the last 2 weeks?

No dryness	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Maximal imaginable dryness

2. How severe has your **fatigue** been during the last 2 weeks?

No fatigue	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Maximal imaginable fatigue

3. How severe has your **pain** (joint or muscular pains in your arms or legs) been during the last 2 weeks?

No pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	Maximal imaginable pain

Domain (weight)	grading
Constitutional (3)	No=0 Low=1 Mod=2
LAD (4)	No=0 Low=1 Mod=2 High=3
Glandular (2)	No=0 Low=1 Mod=2
Articular (2)	No=0 Low=1 Mod=2 High=3
Cutaneous (3)	No=0 Low=1 Mod=2 High=3
Pulmonary (5)	No=0 Low=1 Mod=2 High=3
Renal (5)	No=0 Low=1 Mod=2 High=3
Muscular (6)	No=0 Low=1 Mod=2 High=3
PNS (5)	No=0 Low=1 Mod=2 High=3
CNS (3)	No=0 Low=1 Mod=2
Hematological (2)	No=0 Low=1 Mod=2 High=3
Biological (1)	No=0 Low=1 Mod=2

MCID ≥ 3
Entry criteria or SjS RCTs: ≥ 5

ESSDAI
0-123

Seror R et al, Ann Rheum Dis 2010; 69:1103-9
Seror R et al. Arthritis Care Res (Hoboken) 2013 Aug;65(8):1358-64. doi: 10.1002/acr.21991.
Seror R, et al. RMD Open, 2015 Feb 20;1(1):e000022. doi: 10.1136/rmdopen-2014-000022. eCollection 2015.

ESSDAI Domains: Constitutional and LAD

Domain	Activity level	Description
Constitutional *Exclusion of fever of infectious origin and voluntary weight loss*	No=0	Absence of the following symptoms
	Low=3	Mild or intermittent fever (37.5–38.5°C)/night sweats and/or involuntary weight loss of 5–10% of body weight
	Moderate=6	Severe fever (>38.5°C)/ night sweats and/or involuntary weight loss of >10% of body weight

Domain	Activity level	Description
Lymphadenopathy and lymphoma *Exclusion of infection*	No=0	Absence of the following features
	Low=4	Lymphadenopathy ≥1 cm in any nodal region or ≥2 cm in inguinal region
	Moderate=8	Lymphadenopathy ≥2 cm in any nodal region or ≥3 cm in inguinal region, and/ or splenomegaly (clinically palpable or assessed by imaging)
	High=12	Current malignant B-cell proliferative disorder

ESSDAI: Glandular and Joints

Domain	Activity level	Description
Glandular *Exclusion of stone or infection*	No=0	Absence of glandular swelling
	Low=2	Small glandular swelling with enlarged parotid (≤3 cm), or limited submandibular (≤2 cm) or lachrymal swelling (≤1 cm)
	Moderate=4	Major glandular swelling with enlarged parotid (>3 cm), or important submandibular (>2 cm) or lachrymal swelling (>1 cm)

Domain	Activity level	Description
Articular *Exclusion of osteoarthritis*	No=0	Absence of currently active articular involvement
	Low=2	Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min)
	Moderate=4	1–5 (of 28 total count) synovitis
	High=6	≥6 (of 28 total count) synovitis

ESSDAI Domains: Cutaneous and Pulmonary

Domain	Activity level	Description
Cutaneous *Rate as 'No activity' stable long-lasting features related to damage*	No=0	Absence of currently active cutaneous involvement
	Low=3	Erythema multiforma
	Moderate=6	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
	High=9	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis

Domain	Activity level	Description
Pulmonary *Rate as 'No activity' stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use, etc)*	No=0	Absence of currently active pulmonary involvement
	Low=5	Persistent cough **due to** bronchial involvement with no radiographic abnormalities on radiography Or radiological or HRCT evidence of interstitial lung disease with: no breathlessness and normal lung function test
	Moderate=10	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NHYA II) or abnormal lung function tests restricted to: 70% >DL_{CO} ≥40% or 80% >FVC≥60%
	High=15	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA III, IV) or with abnormal lung function tests: DL_{CO} <40% or FVC <60%

FVC, forced vital capacity; HRCT, high-resolution CT; NYHA, New York Heart Association.

ESSDAI Domains: Renal

Domain	Activity level	Description
Renal *Rate as 'No activity' stable long-lasting features related to damage and renal involvement not related to the disease.* *If biopsy has been performed, please rate activity based on histological features first*	No=0	Absence of currently active renal involvement with proteinuria <0.5 g/day, no haematuria, no leucocyturia, no acidosis or long-lasting stable proteinuria due to damage
	Low=5	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without haematuria or renal failure (GFR ≥60 mL/min)
	Moderate=10	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 mL/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without haematuria or renal failure (GFR ≥60 mL/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High=15	Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/day, or haematuria or renal failure (GFR <60 mL/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinemia related renal involvement

GFR, glomerular filtration rate.

ESSDAI Domains: Muscular and CNS

Domain	Activity level	Description
Muscular *Exclusion of weakness due to corticosteroids*	No=0	Absence of currently active muscular involvement
	Low=6	Mild active myositis shown by abnormal EMG, MRI* or biopsy with no weakness and creatine kinase (N≤CK≤2N)
	Moderate=12	Moderately active myositis proven by abnormal EMG, MRI* or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N<CK≤4N),
	High=18	Highly active myositis shown by abnormal EMG, MRI* or biopsy with weakness (deficit ≤3/5) or elevated creatine kinase (>4N)

*We decided to add this item not included in the initial version since the value of this examination for the diagnosis of myositis was not clear until recently.
EMG, electromyogram.

Domain	Activity level	Description
CNS *Rate as 'No activity' stable long-lasting features related to damage or CNS involvement not related to the disease*	No=0	Absence of currently active CNS involvement
	Moderate=10	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment
	High=15	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischaemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit

ESSDAI Domains: PNS

Domain	Activity level	Description
PNS *Rate as 'No activity' stable long-lasting features related to damage or PNS involvement not related to the disease*	No=0	Absence of currently active PNS involvement
	Low=5	Mild active PNS involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia **Proven small fibre neuropathy*
	Moderate=10	Moderately active PNS involvement shown by NCS, such as axonal sensory–motor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5 or mild ataxia) Or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia)
	High=15	Highly active PNS involvement shown by NCS, such as axonal sensory–motor neuropathy with motor deficit ≤3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤3/5 or severe ataxia

*We decided to add this item not included in the initial version since the link between this entity and SS was not clear until recently.
CIPD, chronic inflammatory demyelinating polyneuropathy; NCS, nerve conduction study.

ESSDAI Domains: Hematologcal and Biological

Domain	Activity level	Description
Haematological *For anaemia, neutropenia, and thrombopenia, only auto-immune cytopenia must be considered Exclusion of vitamin or iron deficiency, drug-induced cytopenia*	No=0	Absence of autoimmune cytopenia
	Low=2	Cytopenia of autoimmune origin with neutropenia (1000<neutrophils<1500/mm^3), and/or anaemia (10<haemoglobin<12 g/dL), and/or thrombocytopenia (100 000<platelets<150 000/mm^3) Or lymphopenia (500<lymphocytes<1000/mm^3)
	Moderate=4	Cytopenia of autoimmune origin with neutropenia (500≤ neutrophils ≤1000/mm^3), and/or anaemia (8≤ haemoglobin ≤10 g/dL), and/or thrombocytopenia (50 000 ≤ platelets ≤100 000/mm^3) Or lymphopenia (≤500/mm^3)
	High=6	Cytopenia of autoimmune origin with neutropenia (neutrophils<500/mm^3), and/or or anaemia (haemoglobin<8 g/dL) and/or thrombocytopenia (platelets<50 000/mm^3)

Domain	Activity level	Description
Biological	No=0	Absence of any of the following biological feature
	Low=1	Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) and/or hypergammaglobulinemia or high IgG level between 16 and 20 g/L
	Moderate=2	Presence of cryoglobulinemia and/or hypergammaglobulinemia or high IgG level >20 g/L, and/or recent onset hypogammaglobulinemia or recent decrease of IgG level (<5 g/L)

Risk Factors for Developing Lymphoma in SjS

- Risk for B cell Lymphoma 15-20x vs gen pop lifetime risk (5-10%)
- Attributed to chronic B-cell activation; mechanisms unknown: chromosomal translocations, mutations of the tumor suppressor gene p53; aberrant immune mechanisms
- Mostly mucosal associated lymphoid tissue (MALT) in salivary glands (1000 fold in SjS); aggressive B-cell non-Hodgkin's lymphoma
- Series form U of Athens identified: +Ro/La/RF; ↓C4; Salivary gland enlargement, LAD, RP, monoclonal gammopathy → The probability of NHL development was 3.8% for patients presenting with ≤2 risk factors, 39.9% for those having 3 to 6 risk factors and reached 100% in the presence of all 7 risk factors

EVERY 1-2 YEARS: CBCD, SPEP,UPEP, RF, C3,C4, CRYOGLOBULINS

IF HIGH RISK, MONITOR EVERY 6 MONTHS
GOOD PHYSICAL EXAM

Fragkioudaki et al Medicine (Baltimore). 2016 Jun; 95(25): e3766

SjS Treatment: Need for DEI!!!

- No FDA approved treatments
- Thought that SjS is a benign disease; “Fibro fear”
- Unconscious bias that it is mostly secondary to other CTDs
- Heterogeneous disease: timeline of progression to extraglandular manifestation unknown
- Often highly symptomatic SjS don’t have internal organ involvement, while low sicca (who don’t search care) do
- No available solid registries in the US; different than European SjS
- Fear of lymphoma
- Lack of a robust, sensitive-to-change, outcome measure
- Treatment currently relies on sialagogues and organ-directed therapies borrowed from SLE/CLE, RA, ILD

Managing Xerostomia

- Oral hygiene; avoid alcohol and smoking (reduce periodontal disease)
- Saliva replacement products, Sugar free chewing gum

- Sialagogues/Muscarinic agonists for pts with reduced salivary gland function
  - Multiple placebo controlled trials showing improved salivary flow(3)
- Pilocarpine 5mg every 6 hrs (1)
- Cevimeline 30mg every 8 hrs (2)
  - Best doses in balancing efficacy and side effects(3)

- N –Acetyl cysteine may be an alternative (4)
  - Small open label trial: 26 pts, improved ocular soreness, irritability, halitosis, thirst,

1.Vivino FB. Arch Intern Med 1999; 159:174–181.
2.Petrone D.Arthritis Rheum 2002; 46: 748–754.
3.Ramos-Casals. JAMA 2010;304(4)452-460
4.Walters, MT. Scand J Rheumatol suppl 1986;61,253-8

Managing Xerophtalmia

- Preservative-free tear substitutes for daily use
- Ocular lubricating ointments at night

- Immunomodulatory:
  - CSA 0.05% twice daily topical for moderate to severe dry eye(1,4)

- Punctal plugs(2)
- Systemic rx –Pilocarpine(3)
- Topical NSAIDS or topical corticosteroids reserved for severe refractory ocular dryness- should be prescribed by ophthalmologists(Marsh)

1.Leonardi A. Eur JOphthalmol 2016; 26: 287–296
2.Foulks GN,. Ocul Surf 2015;13: 118–132
3.Vivino FBArch Intern Med 1999; 159:174–181.
4. Ramos-Casals. JAMA 2010;304(4)452-460

Systemic SjS Treatment

- Commonly used Rx: HCQ, MTX, AZA, CSA

- HCQ open label studies positive results
- HCQ in a RCT no benefits(1)
  - 19pts, 2 yr crossover, HCQ 400mg/day
  - Fatigue, myalgia, parotid enla arthralgiargement
  - NS vs placebo
- HCQ in pSS, prospective study 14 pts
  - No effect on sicca sxs/fatigue
  - ESR better, CRP better, IgG better ($p<0.05$) in all
- JOCQUER trial (5) 214: 120 patients with no systemic complications; PBO vs. 400 mg; 6 mo
  - primary composite end point of a ≥30% reduction in dryness, pain and fatigue

- Anti TNF RCT: Etanercept (3), Infliximab(3) Not effective

1.Kruize AA, Ann Rheum dis. 1993;52(5):360-364
2. Tishler M. Ann Rheum dis. 1999;58(4):253-256
3. Sankar A&R 2004; 50(7):2240-2245
4. Mariette A&R 2004; 50(4):1270-1276
5. Gottenberg, J.-E. et alJAMA 312, 249–258 (2014).

Box 2 | **EULAR recommendations for the management of primary Sjögren syndrome**

Overarching principles

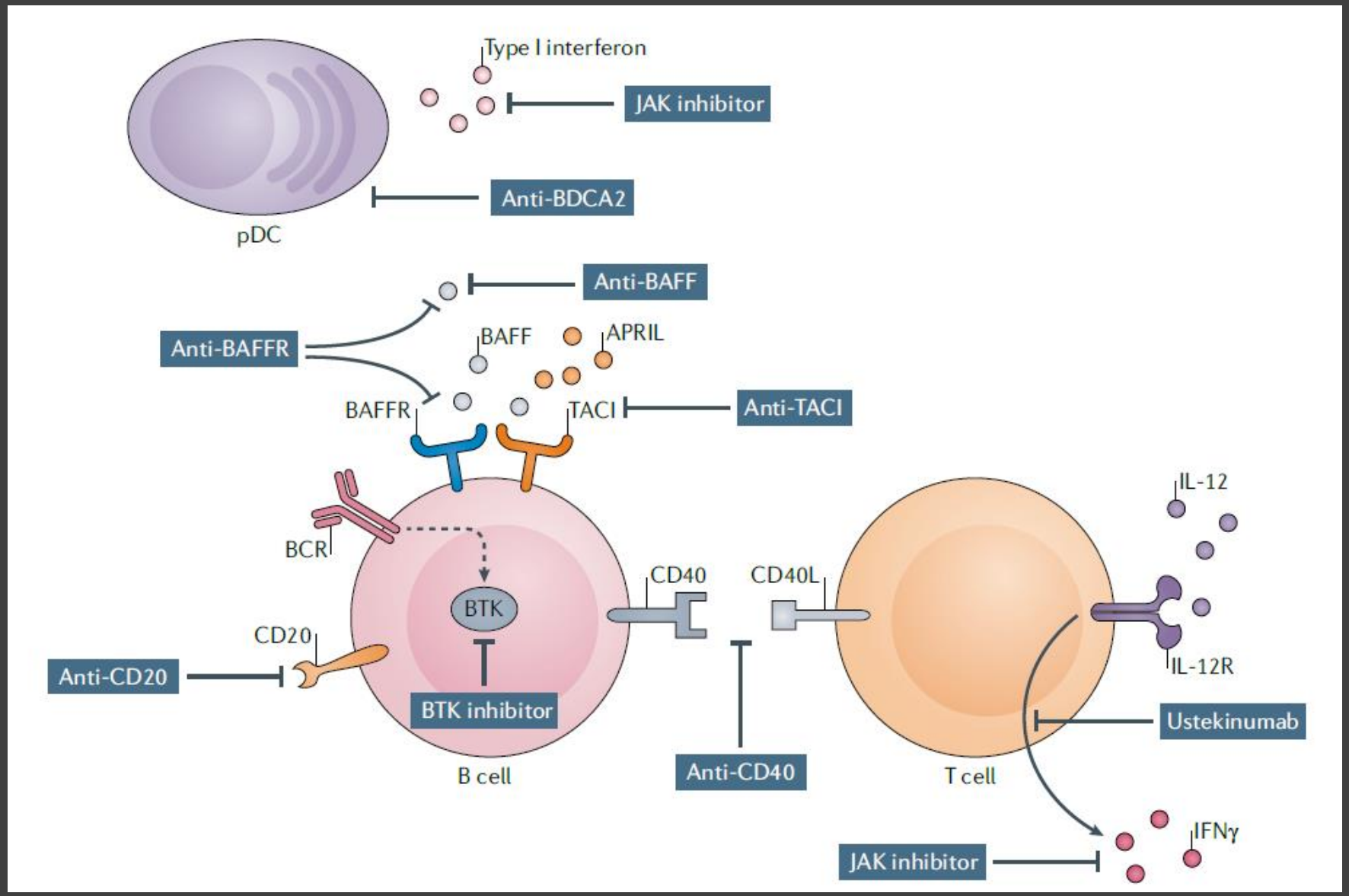
- Patients with Sjögren syndrome should be managed at, or in close collaboration with, centres of expertise following a multidisciplinary approach.
- The first therapeutic approach for dryness should be symptomatic relief using topical therapies.
- Systemic therapies may be considered for the treatment of active systemic disease.

Individual recommendations

- Baseline evaluation of salivary gland function is recommended before starting treatment for oral dryness.
- The preferred first therapeutic approach for oral dryness according to salivary gland function may be:
  - Non-pharmacological stimulation for mild dysfunction
  - Pharmacological stimulation for moderate dysfunction
  - Saliva substitution for severe dysfunction
- The first-line therapeutic approach to ocular dryness includes the use of artificial tears and ocular gels or ointments.
- Refractory or severe ocular dryness may be managed using topical immunosuppressive-containing drops and autologous serum eye drops.
- Concomitant diseases should be evaluated in patients presenting with fatigue or pain, whose severity should be scored using specific tools.
- Consider analgesics or other pain-modifying agents for musculoskeletal pain, considering the balance between potential benefits and adverse effects.
- Treatment of systemic disease should be tailored to organ-specific severity using the EULAR Sjögren's Syndrome Disease Activity Index definitions.
- Glucocorticoids should be used at the minimum dose and length of time necessary to control active systemic disease.
- Immunosuppressive agents should be mainly used as glucocorticoid-sparing agents, with no evidence supporting the choice of one agent over another.
- B cell-targeted therapies may be considered in patients with severe, refractory systemic disease.
- The systemic organ-specific therapeutic approach may follow, as a general rule, the sequential (or combined) use of glucocorticoids, immunosuppressive agents and biologic agents.
- Treatment of B cell lymphoma should be individualized according to the specific histological subtype and disease stage.

Ramos- Casals, M. et al. Ann. Rheum. Dis. 79, 3–18 (2020).

Therapeutic Targets



Trials Using Non-Validated Outcomes

Agent	Target	Comparator	Number of participants	Primary end point	Was the primary end point met?	Ref.
Etanercept	TNF	Placebo	14	A ≥20% improvement for two of three domains (subjective or objective measures of dry mouth, subjective or objective measures of dry eyes and IgG level or ESR) from baseline to week 12	No	36
Infliximab	TNF	Placebo	103	A ≥30% improvement in scores on two of three VAS (measuring joint pain, fatigue and dryness (buccal, ocular, skin, vaginal or bronchial)) at week 10	No	35
Anakinra	IL-1	Placebo	26	Difference in Fatigue Severity Scale and fatigue VAS scores between groups at week 4	No	38
Rituximab	CD20	Placebo	17	A 20% reduction in fatigue VAS scores at week 24	No	48
Rituximab	CD20	Placebo	30	Improvement in SWSFR at weeks 5, 12, 24 and 48	Yes; significant improvements at week 5 ($P=0.018$) and week 12 ($P=0.004$)	49
Rituximab	CD20	Placebo	120	A 30 mm improvement in scores on two of four VAS (measuring global disease, pain, fatigue and dryness) at week 24	No, but there were significant improvements in scores on the fatigue VAS at week 6 ($P<0.001$) and week 16 ($P=0.012$) (secondary end point)	43
Rituximab	CD20	Placebo	133	A 30% improvement in scores on the fatigue VAS or oral dryness VAS at week 48	No, but modest effect on unstimulated saliva flow rate (secondary end point)	14
Baminercept	Lymphotoxin	Placebo	72	Change in SWSFR from baseline to week 24	No, and no significant effect on ESSDAI score (secondary end point)	84

Non-validated outcomes are mainly patient-related outcomes or salivary flow, which have never been validated as pertinent outcomes. ESR, erythrocyte sedimentation rate; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; SWSFR, stimulated whole saliva flow rate; VAS, visual analogue scale.

Seror et al Nat Rev Rheumatol 2021 Aug;17(8):475-486.
doi: 10.1038/s41584-021-00634-x

Belimumab: BAFFi

- BELISS: Efficacy and safety of belimumab in primary Sjögren's syndrome: open lable phase II
- 30 patients with pSS , +anti- SSA/Ro antibodies and had one of the following: current systemic complications or salivary gland enlargement; early disease (<5 years); or biomarkers of B cell activation.
- primary outcome: improvement in two of five items (pain, fatigue, dryness, systemic disease activity assessed by the physician and B cell activity biomarkers) at week 28
- Was met by 60% of the participants
- No RCT has yet been conducted, but evaluation of new strategies in which belimumab and rituximab are combined is currently ongoing

Mariette, X. et al. *Ann. Rheum. Dis.* **74**,526–531 (2015).

Trials Using Validated Outcomes (1)

Trial identifier	Agent(s)	Target	Comparator	Number of participants	Inclusion criteria	Primary end point	Results
EUCTR2014-003140-12-NL	Leflunomide and hydroxychloroquine	Cell metabolism, autophagy and TLR signalling	Placebo	29	ESSDAI score ≥5; positive labial salivary gland biopsy	Change in ESSDAI score from baseline to week 24	Significant improvement in ESSDAI score ($P=0.0078$)
NCT01782235 (ETAP)	Tocilizumab	IL-6R	Placebo	110	ESSDAI score ≥5; positive for anti-SSA/Ro antibodies	Improvement in ESSDAI score of ≥3 points from baseline to week 24	No difference in primary end point between active treatment and placebo
NCT02631538	Belimumab and rituximab co-administration	BAFF and CD20	Placebo	70	ESSDAI score ≥5; positive for anti-SSA/Ro or anti-SSB/La antibodies; UWSFR >0	Number of participants with SAEs at week 68	Completed, results not available
NCT02149420	Ianalumab (VAY736)	BAFFR	Placebo	27	ESSDAI score ≥6; ANA (titre ≥1:160); positive for RF or anti-SSA/Ro or anti-SSB/La antibodies; SWSFR >0	Change in ESSDAI score from baseline to week 12	Predefined criteria for primary end point not met, but showed a trend towards positive effect versus placebo
NCT04078386	RC18	TACI	Placebo	42	ESSDAI score ≥5; positive for anti-SSA/Ro antibodies	Change in ESSDAI score from baseline to week 24	Active, not recruiting
NCT02291029	Iscalimab (CFZ533)	CD40	Placebo	12 (cohort 1) and 32 (cohort 2)	ESSDAI score ≥6; positive for anti-SSA/Ro antibodies or ANA (titre ≥1:160) and RF positive; SWSFR >0	Change in ESSDAI score from baseline to week 12	Significant improvement in ESSDAI score ($P=0\cdot009$) with i.v. iscalimab
NCT03905525 (TWINSS)	Iscalimab (CFZ533)	CD40	Placebo	260 (split over two cohorts)	Positive for anti-SSA/Ro antibodies (both cohorts); SWSFR >0 (both cohorts); ESSDAI score and ESSPRI score ≥5 (cohort 1); ESSDAI score <5 and ESSPRI (fatigue or dryness) score ≥5 (cohort 2)	Change in ESSDAI score from baseline to week 24 (cohort 1); change in ESSPRI score from baseline to week 24	Recruiting

Trials Using Validated Outcomes

NCT04572841	SAR441344	CD40L	Placebo	88	Positive for anti-SSA/Ro antibodies; SWSFR ≥0.1; ESSDAI score ≥5; disease duration ≤7 years	Change in ESSDAI score from baseline to week 12	Recruiting
NCT04035668	LOU064	BTK	Placebo	252 (dose-ranging study)	ESSDAI score ≥5; ESSPRI score ≥5; positive for anti-SSA/Ro antibodies; UWSFR >0	Change in ESSDAI score from baseline to week 24	Recruiting

Trial identifier	Agent(s)	Target	Comparator	Number of participants	Inclusion criteria	Primary end point	Results
NCT02610543	Seletalisib (UCB5857)	PI3K	Placebo	58 (aim), only 27 enrolled	ESSDAI score ≥5; positive for anti-SSA/Ro or anti-SSB/La antibodies; UWSFR >0; salivary gland biopsy	Change in ESSDAI score from baseline to week 12	Study terminated early owing to enrolment issues (data from 20 patients analysed); trend for improvement in ESSDAI and ESSPRI scores
NCT02334306	MEDI5872 (AMG557)	ICOSL	Placebo	42 (aim), only 32 enrolled	ESSDAI score ≥6; positive for anti-SSA/Ro or anti-SSB/La antibodies and IgG titre >16 g/l or positive for RF	Change in ESSDAI score from baseline to week 12	No significant improvement in ESSDAI score compared with placebo
NCT02067910 (ASAP-III)	Abatacept	CTLA4	Placebo	80	ESSDAI score ≥5; disease duration ≤7 years; positive parotid gland biopsy	Change in ESSDAI score from baseline to week 24	No significant improvement in ESSDAI score compared with placebo or in secondary end points (except IgG and RF concentrations)
NCT02915159	Abatacept	CTLA4	Placebo	187	ESSDAI score ≥5; positive for anti-SSA/Ro antibodies	Change in ESSDAI score from baseline to week 24	No significant improvement in ESSDAI score compared with placebo
NCT04496960	Tofacitinib	JAK1 and JAK3	Placebo	30	ESSDAI score between 2 and 13; SWSFR >0	Safety and tolerability	Recruiting

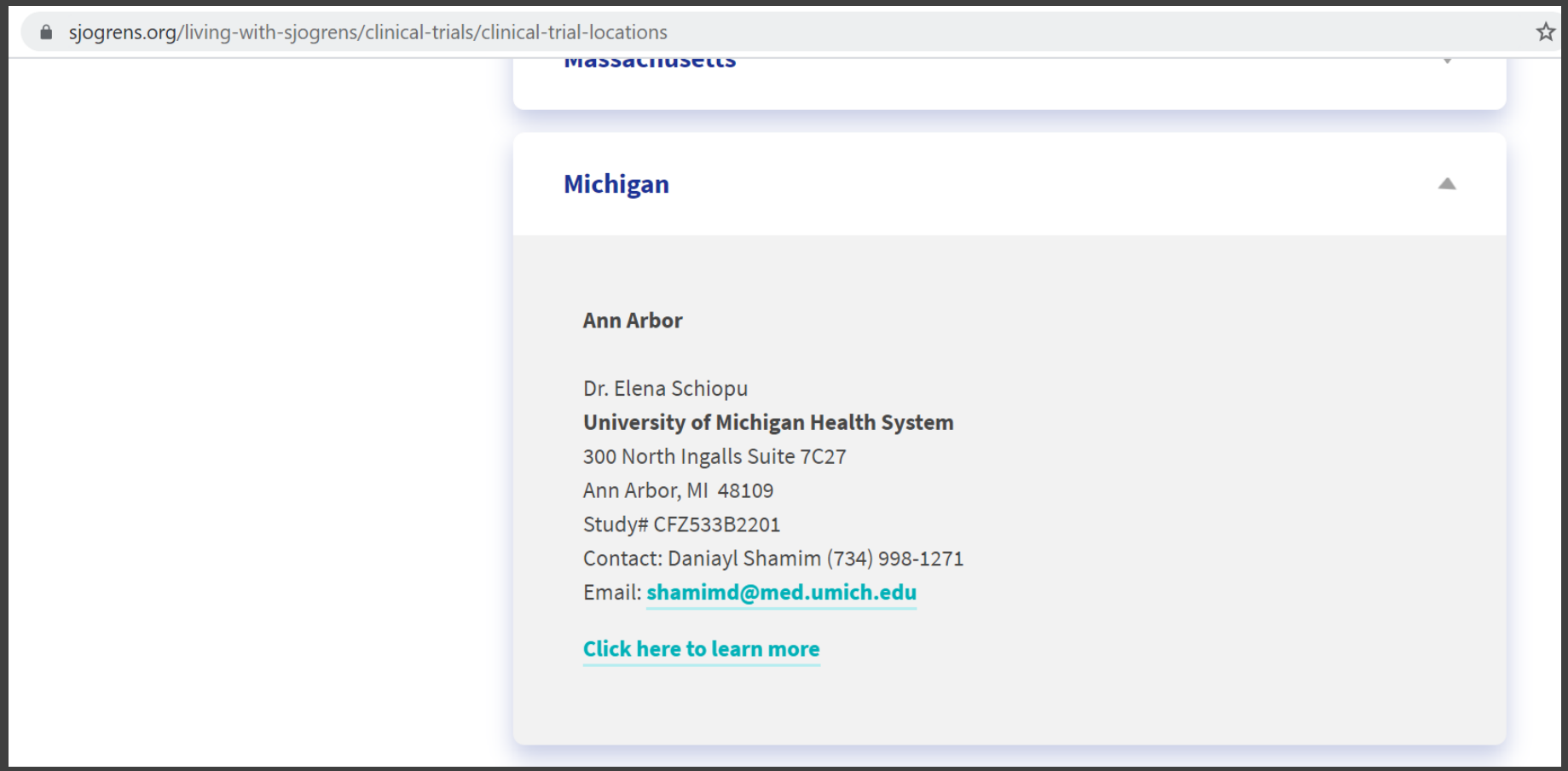
Trials Using Non-Validated Outcomes

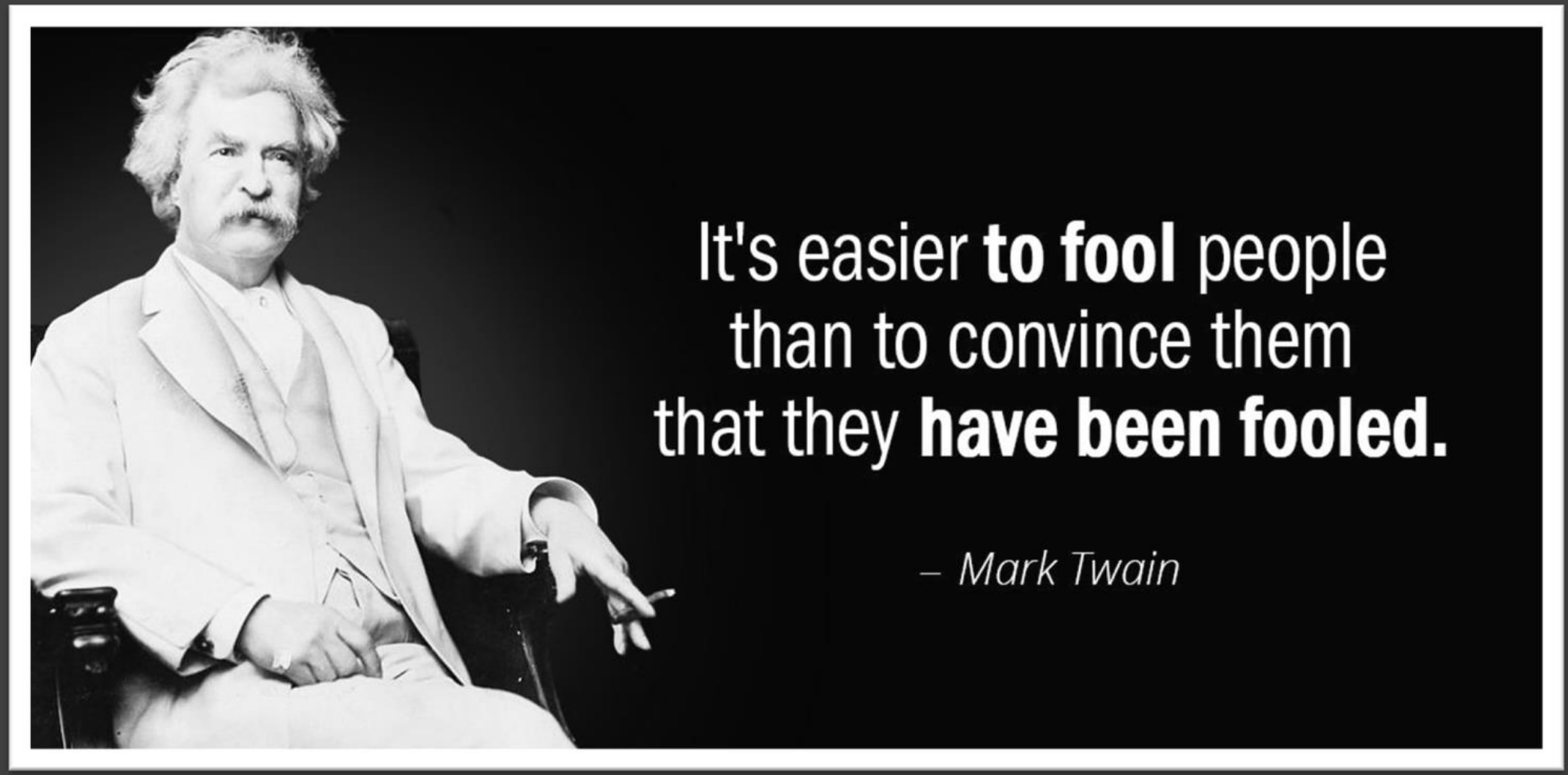
Agent	Target	Comparator	Number of participants	Primary end point	Was the primary end point met?	Ref.
Etanercept	TNF	Placebo	14	A ≥20% improvement for two of three domains (subjective or objective measures of dry mouth, subjective or objective measures of dry eyes and IgG level or ESR) from baseline to week 12	No	36
Infliximab	TNF	Placebo	103	A ≥30% improvement in scores on two of three VAS (measuring joint pain, fatigue and dryness (buccal, ocular, skin, vaginal or bronchial)) at week 10	No	35
Anakinra	IL-1	Placebo	26	Difference in Fatigue Severity Scale and fatigue VAS scores between groups at week 4	No	38
Rituximab	CD20	Placebo	17	A 20% reduction in fatigue VAS scores at week 24	No	48
Rituximab	CD20	Placebo	30	Improvement in SWSFR at weeks 5, 12, 24 and 48	Yes; significant improvements at week 5 ($P = 0.018$) and week 12 ($P = 0.004$)	49
Rituximab	CD20	Placebo	120	A 30 mm improvement in scores on two of four VAS (measuring global disease, pain, fatigue and dryness) at week 24	No, but there were significant improvements in scores on the fatigue VAS at week 6 ($P < 0.001$) and week 16 ($P = 0.012$) (secondary end point)	43
Rituximab	CD20	Placebo	133	A 30% improvement in scores on the fatigue VAS or oral dryness VAS at week 48	No, but modest effect on unstimulated saliva flow rate (secondary end point)	14
Baminercept	Lymphotoxin	Placebo	72	Change in SWSFR from baseline to week 24	No, and no significant effect on ESSDAI score (secondary end point)	84

Non-validated outcomes are mainly patient-related outcomes or salivary flow, which have never been validated as pertinent outcomes. ESR, erythrocyte sedimentation rate; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; SWSFR, stimulated whole saliva flow rate; VAS, visual analogue scale.

Clinical Trials Are a Therapeutic Option for SjS patients

- Partnering with SSF, Pharma, Ophtalmologists, Institutional resources




It's easier **to fool** people
than to convince them
that they **have been fooled.**
– *Mark Twain*

Thank you