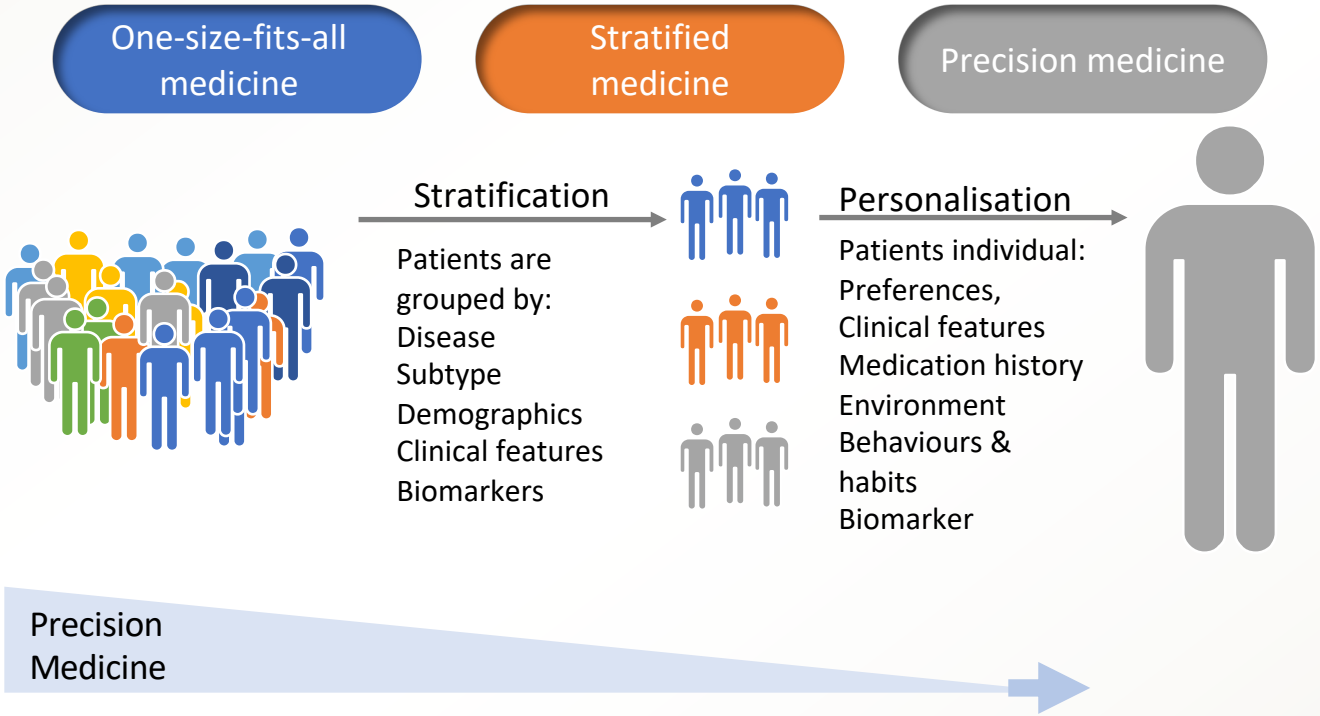
National University of Athens
Greece

Management of Sjögren's Disease

Andreas V Goules, MD

Dept. of Pathophysiology
Medical School

Sjögren's Disease
Management
Precision Medicine vs Traditional Medicine



Sjögren's Disease
Management

General Principles

- Estimate disease characteristics
  - Extent, severity, damage
  - ***High vs low risk for lymphoma***

- Treatment strategy and escalation plan
  - Age
  - Sex
  - Co-morbidities
  - ***Patient's personal preference***

- Educate and inform patients
  - Prognosis
  - Course
  - Complications
  - Discuss all therapeutic options (risk/benefit)

Ramos-Casals et al. Ann Rheum Dis 2020
Brito-Zeron et al. RMD open 2019

Sjögren's Disease
Management

Overview

- Non pharmacologic interventions and preventive measures
- Local treatments
- Conventional and organ based treatments
- Targeted therapies

Ramos-Casals et al. Ann Rheum Dis 2020
Brito-Zeron et al. RMD open 2019

Sjögren's Disease
Management

Non pharmacologic interventions and preventive measures

- Self-care for oral and ocular dryness
  - Hydration
  - Avoidence of certain medications
  - Oral hygiene and regular visits
  - Mechanical stimulation (e.g. suger free gums)
  - Tears conservation (physical barriers)

- Lifestyle modifications

- Vaccinations
  - HBV
  - Pneumonococcus
  - Seasonal flu
  - Herpes zoster (non-live formulation)

Ramos-Casals et al. Ann Rheum Dis 2020

Brito-Zeron et al. RMD open 2019

Sjögren's Disease
Management

Local treatments

- Oral dryness
  - Muscarinic agonists
    - pilocarpine or cevimeline
  - Rescue therapies
    - mucolytic agents
  - Saliva substitution (gels, sprays, rinses)
- Ocular dryness
  - Volume replacement and lubrication
    - artificial tears (eye drops)
  - Lubricants (ointments, gels)
  - Topical NSAIDs/corticosteroids
  - Topical Cyclosporine
  - Tear canal plug insertion

Ramos-Casals et al. Ann Rheum Dis 2020

Brito-Zeron et al. RMD open 2019

Sjögren's Disease
Management

Organ based treatments

Glandular Involvement

- Glucocorticoids (0.3 mg/kg/day) for 2-3 weeks
- Rx or belimumab

Articular Involvement

- Corticosteroids (5-7.5mg/daily)
- Hydroxychloroquine
- Methotrexate (10-15mg/weekly)
- Leflunomide (20mg/daily)
- Rituximab

Cutaneous Involvement

- Glucocorticoids (0.3-1 mg/kg/day)
- HQ plus MTX or colchicine or AZA or MMF
- Dapsone or thalidomide or lenalidomide

} Annular rash

- HQ plus colchicine
- GC (0.5-1mg/kg) + Rx or CYC ± PE

} CV Purpura Ulcers Ischemia Necrosis

Ramos-Casals et al. Ann Rheum Dis 2020

Brito-Zeron et al. RMD open 2019

Sjögren's Disease
Management

Organ based treatments

Pulmonary Involvement-Small airways

- Short acting beta agonists (SABA) as needed
- Long acting beta agonists (LABA) plus low dose inhaled glucocorticoids (ICS) or long acting muscarinic agonists (LAMA)

} Small Airways Disease

Pulmonary Involvement-ILDs

- Corticosteroids (0.5-1 mg/kg) plus mycophenolate mofetil or azathioprine
- Rituximab or cyclophosphamide

} NSIP, LIP, COP

Ramos-Casals et al. Ann Rheum Dis 2020
Kampolis et al. Autoimmune Rev 2018
Karakontaki et al. Autoimmune Rev 2021

Sjögren's Disease
Management

Organ based treatments

Neurologic-CNS

- 1g iv pulses of methyl-prednisolone x 3 plus oral glucocorticoids (0.5-1 mg/kg/day) plus cyclophosphamide or Rx→ MMF or AZA — Vaculitis, MS-like
- 1g methyl-prednisolone x 5 days →rituximab, mycophenolate mofetil, azathioprine or eculizumab — NMO

Neurologic-PNS

- Oral glucocorticoids (0.5-1 mg/kg/day) plus Rx or cyclophosphamide ± PE
- 1g iv pulses of methyl-prednisolone x 3 (motor element)

— Axonal PNS

- channel alpha 2 delta anticonvulsant agonists (gabapentin, pregabalin) — Small fiber PNS, Mild sensory PNS
- IVIG or Rx or CYC or PE → CIDP, gangionopathy

Ramos-Casals et al. Ann Rheum Dis 2020

Pavlakis. J Neuroo Neurosurg Psych 2011

Sjögren's Disease
Management

Organ based treatments

Interstitial Nephritis

- Alkali supplements (1-2m Eq/Kg) — dRTA
- Alkali supplements plus 12.5-25mg/daily HCZ — pRTA
- Potassium plus spironolactone — Hypokalemia
- Immunosuppression? — Renal Insufficiency tubulitis
  - Short course GC

Glomerulopathy

- Oral glucocorticoids (0.5-1 mg/kg/day) plus MMF or AZA — Mesangial No renal insuffeciency
- Oral glucocorticoids (0.5-1 mg/kg/day) plus Rx or CYC ± PE — MP Renal insuffeciency

Ramos-Casals et al. Ann Rheum Dis 2020
Goules et al. Medicine 2000, Goules et al. Arthritis Rheum 2013
Goules et al. Clin Exp Rheumatol 2019

Sjögren's Disease

Management-End Points of Clinical Trials

ESSDAI

- Ovreall disease activity
- 12 domains (weight)
- Activity level : no, low, moderate, high (0-3)
- Total score: 0-123
- ClinESSDAI
- Clinical End points
  - Δmean ESSDAI change from baseline between the 2 groups
  - Responders between the 2 groups (Δ ESSDAI ≥ 3points
  - Δmean ESSDAI between the 2 groups

ESSPRI

- Overall PROs
- 3 domains (limb pain, fatigue, dryness)
- VAS: 0-10 numerical scale
- ESSPRI: mean VAS from 3 domains
- Clinical End points
  - Responders: reduction ≥ 15%, 20%, 30% in 1 or 2 domains

Seror et al AnnRheum Dis 2010, Seror et al Ann Rheum 2011
Seror et al Ann Rheum Dis 2015, Seroro et al Ann Rheum Dis 2016

Sjögren's Disease
Management-HQ

JOQUER

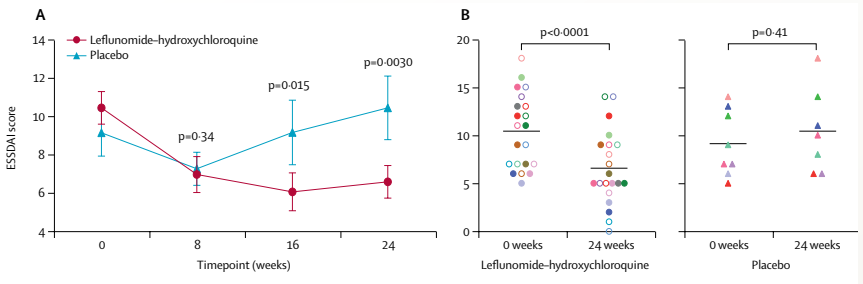
- 56 HQ vs 64 Ppacebo (week 24)
- ≥ 30% reduction in 2 of the 3 numeric analog scale scores at week 24 [0 [best] to 10 [worst]

	No./Total (%)			
	Placebo	Hydroxychloroquine	OR (95% CI)	*P* Value
Without imputation				
Week 24	9/52 (17.3)	9/51 (17.6)	1.02 (0.36-2.87)	.96
Week 48[a]	8/46 (17.4)	11/40 (27.5)	2.60 (0.91-7.40)	.08
After mean of 50 imputations				
Week 24	11/64 (17.2)	10/56 (17.9)	1.01 (0.37-2.78)	.98
Week 48[a]	12/64 (18.8)	17/56 (30.4)	2.06 (0.66-6.43)	.21

- No differences at week 24 (overal and by domain/item)

RepurpSS-I

- 21 HQ+LEF vs 8 placebo
- the mean difference in ESSDAI score, adjusted for baseline values at week 24



- HQ+LEF group: −4·35 points (95% CI −7·45 to −1·25, p=0·0078)

Gottenberg et al. JAMA 2014

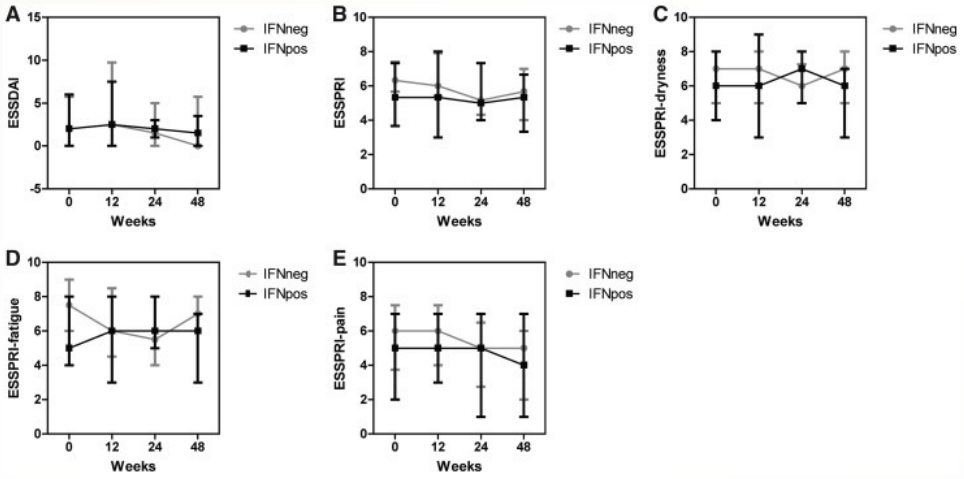
Van der Heijden et al. Lancet Rheumatol 2020

Sjögren's Disease

Management-HQ

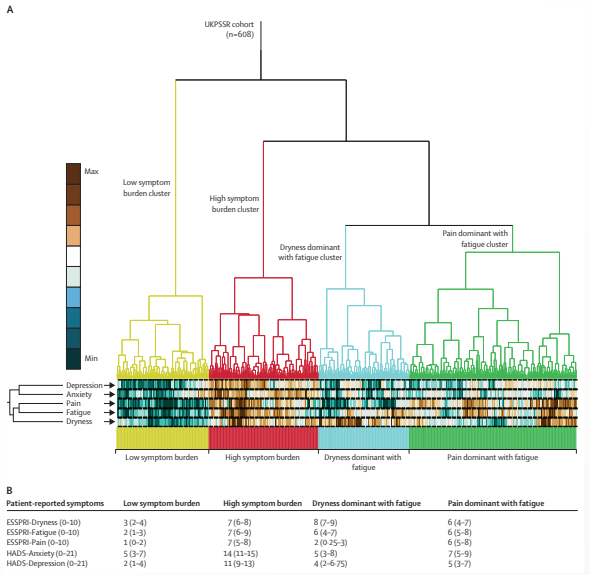
JOQUER-IFN statification

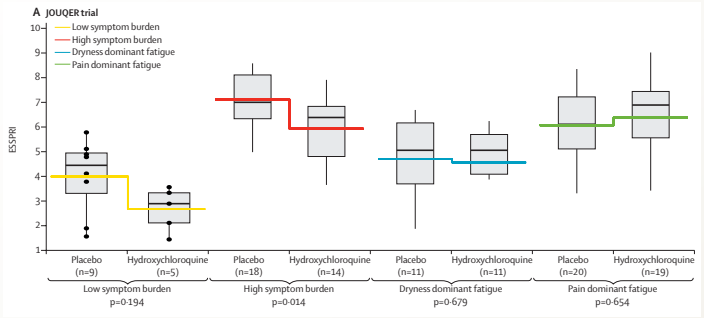
N=77



JOQUER-NSST statification

N=120





Bodewes et al. Rheumatolgy 2020

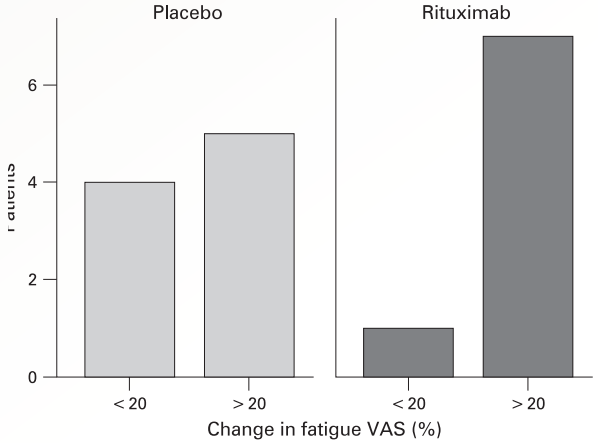
Tarn et al. Lancet Rheumatol 2019

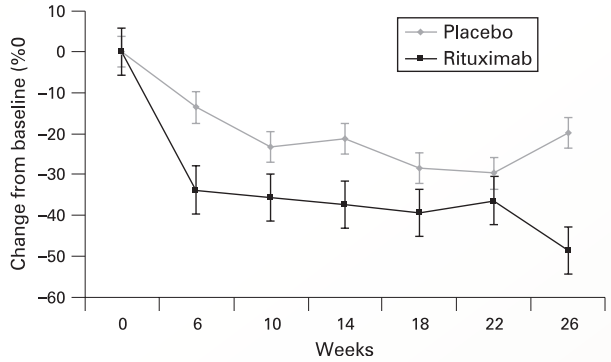
Sjögren's Disease

Management-Rituximab

Dass et al 2008

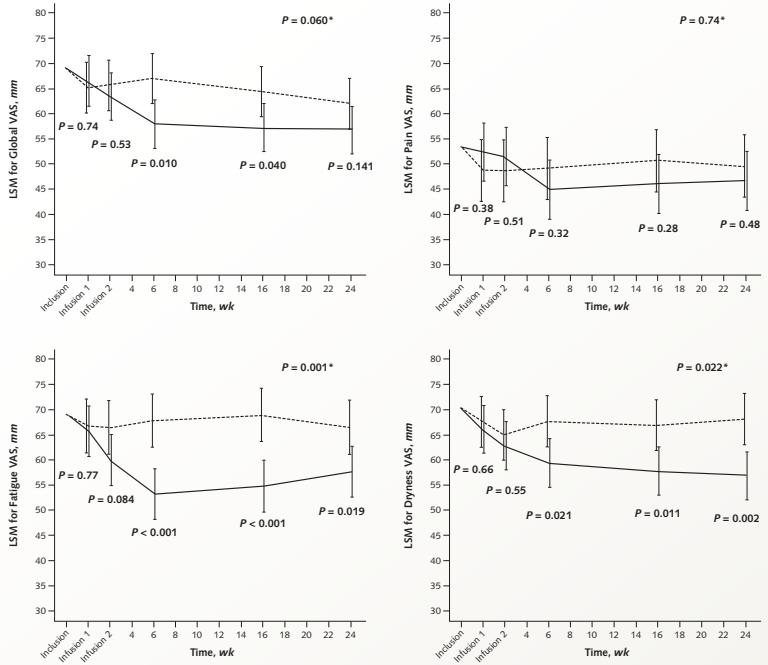
- 17 pSS patients VAS fatigue ≥ 50mm→ Rx vs placebo (1:1), one infusion
- Proportion ≥ 20% reduction in fatigue VAS + change from baseline at 6 months





TEARS

- 120 pSS patients VAS>50 in at least 2 of 4 items (overall, pain, fatigue, dryness) → Rx vs placebo (1:1) (one infusion)
- Improvement of at least 30 mm reduction in 2 of 4 VAS by week 24.



Dass et al. Ann Rheum Dis 2008

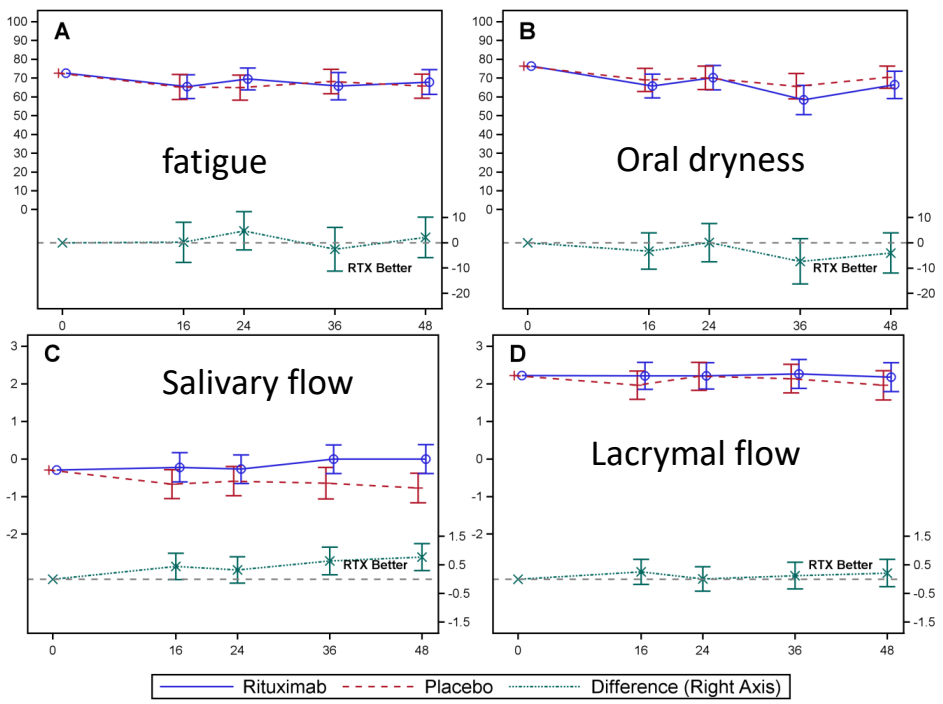
Devauchelle-Pense et al. Ann Intern Med 2014

Sjögren's Disease
Management-Rituximab

TRACTISS

- 67 vs 66 pSS patients with VAS ≥ 50mm in **fatigue and oral dryness** → Rx vs placebo (2 infusions)
- Proportion of 30% reduction in either fatigue or oral dryness at 48 weeks measured by VAS
- Secondary : ESSDAI, ESSPRI, salivary and lachrymal flow at week 48

- No difference regarding the primary end point
- *Only difference the salivary flow and the change from baseline (Figure C)*



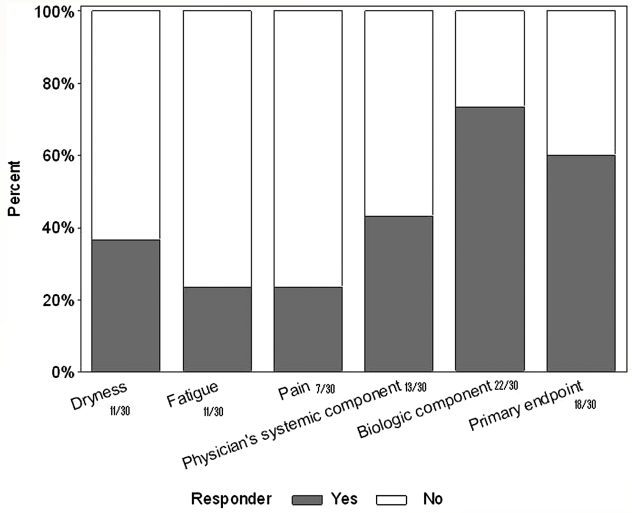
Bowman et al. Arthritis Rheumatol 2017

Sjögren's Disease

Management-Belimumab

BELISS

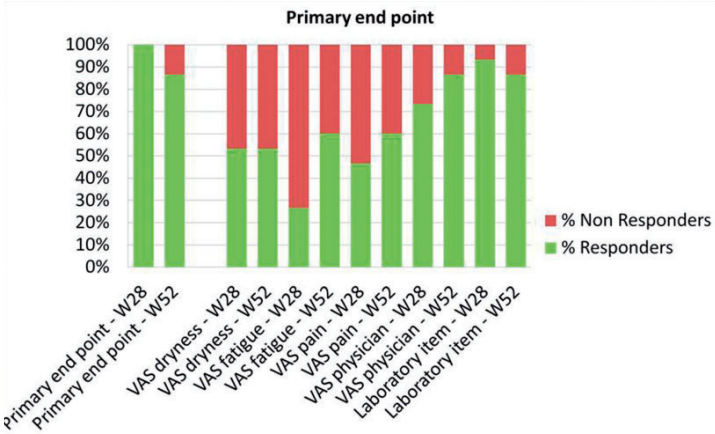
- Open label: 30 pSS patients → Bel (10mg/kg) until week 24
- Primary: 2 of 5 → reduction ≥30% VAS in dryness, fatigue, pain, ≥30% in systemic activity VAS assessed by the physician and/or >25% improvement in any B cell activation biomarker values (at week 24)

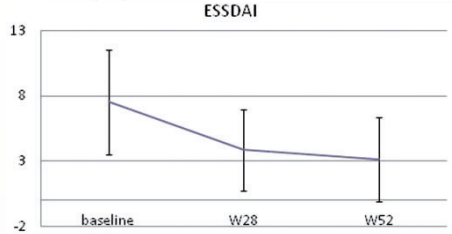


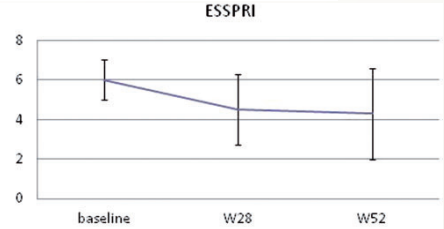
- Changed: ESSDAI and ESSPRI
- Unchanged: salivary flow

Post-BELISS

- Long term effects: 15 responders vs 4 non-responers until week 52
- Re-evaluation at week 52







- Persistent response
- Further improvement: fatigue and ESSDAI

Mariette et al. Ann Rheum Dis 2013

De Via et al Rheumatology 2015

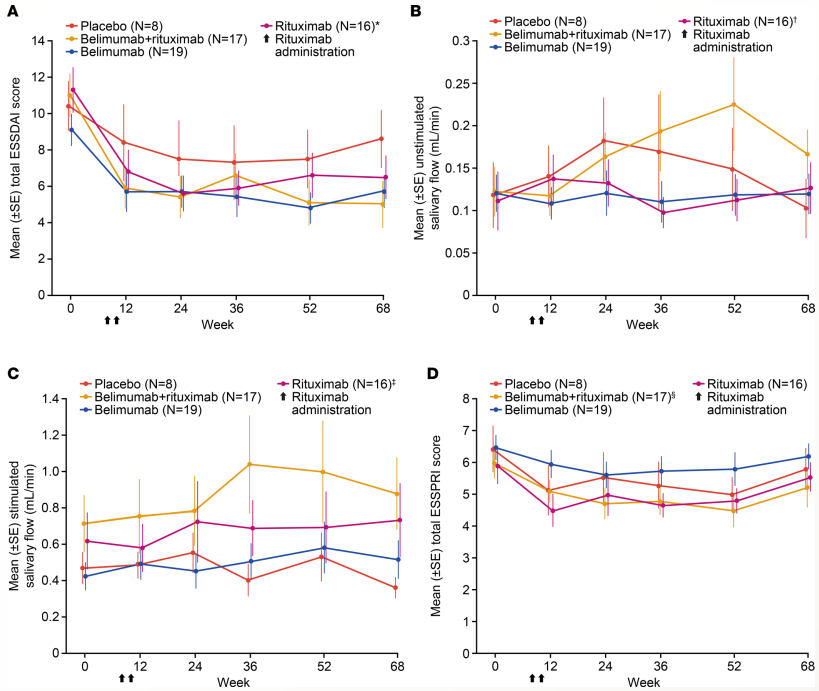
Sjögren's Disease

Management-Sequential/Combinational therapies

- 60 pSS patients ESSDAI ≥ 5 → 1 of 4 arms: placebo, s.c. belimumab, i.v. rituximab, or sequential belimumab + rituximab (week52)
- Outcome (week 68): peripheral B cells, B cells in minor salivary glands (MSGs), CXCL13, safety issues

Results (Bel+Rx)

- Complete B cell depletion in MSG
- Sustained peripheral B cells depletion
- Delayed of peripheral B cell reconstitution
- Trend for mean reduction in ESSDAI, change from baseline, responders and ClinESSDAI and unstimulated salivary flow but not ESSPRI
- No safety issues (infections)



Marriette et al JCI insights 2022

Sjögren's Disease

Inefficacy of Biologic Agents

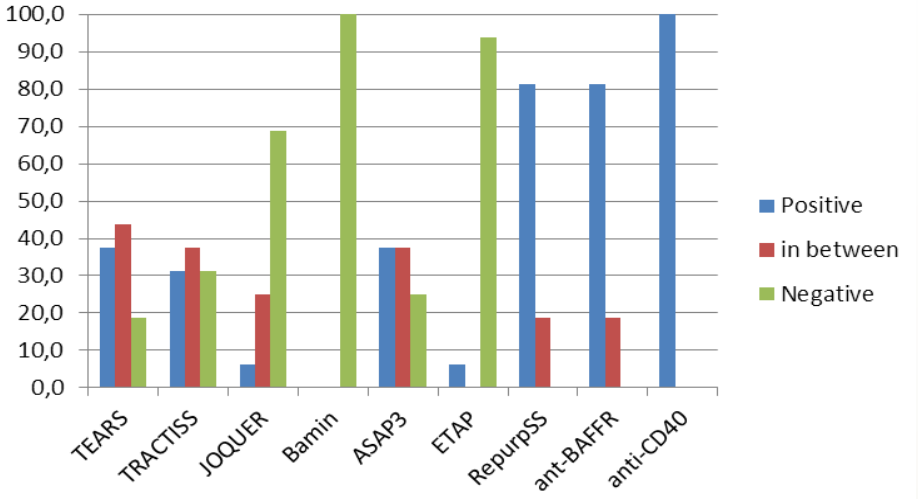
Targeted treatments	Pros	Cons
Rituximab **(anti-CD20 mab)**	• Effective for treating B cell mediated manifestations due to cryoglobulinemia • Can be combined with belimumab for refractory CV • Therapeutic option for arthritis, ILD, NMOSD and hematologic manifestations	• Improvement of disease activity, dryness, fatigue and salivary flow in some studies.
Belimumab **(anti-BAFF-R mab)**	• May be combined with rituximab for refractory CV	• Modest reduction only in dryness, parotid enlargement and arthralgias
TNF inhibitors **(infliximab, etanercept)**	–	• No efficacy in any aspect of the disease
Abatacept **(CTLA4-Ig fusion protein)**	• Evidence of biologic activity and improvement of disease related laboratory parameters	• Lack of clinical efficacy • Relatively higher rates of serious adverse events
Anakinra **(IL-1 receptor antagonist)**	–	• No effect in fatigue
Tocilizumab **(anti-IL6R mab)**	–	• Lack of efficacy
Ianalumab **(anti-monoclonal BAFF-R** **mab, engineered for efficient ADCC)**	• Decreased overall disease activity • Depletion of mature B cells over naive	• Infusion/injection related reactions
Epratuzumab **(anti-CD22 mab)**	• Limited efficacy in tear production, salivary flow and fatigue	• Significant improvement in limited proportion of patients
Iguratimod **(small molecule inhibiting inflammatory pathways including NF-kB)**	• Improved fatigue and dryness • Decreased plasma cells	• No reduction in disease activity • High rates of adverse events
Baminercept **(Lymphotoxin-β receptor fusion protein)**	• Reduced B and T circulating cells • Decreased CXCL13 plasma levels	• No reduction in disease activity, salivary flow rate or dryness • Liver toxicity
Seletasilib **(selective PI3kd inhibitor implicated in B cell signaling)**	• Reduced inflammation in diseased salivary glands	• No reduction in disease activity salivary flow or tear production • High rates of adverse events

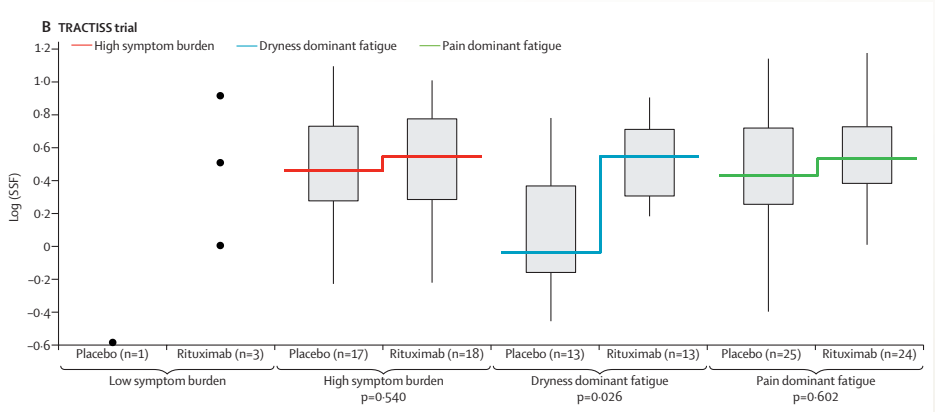
Dass et al. Ann Rheum Dis 2008, Bowman et al Arthritis `Rheumatol 2017, De Vita et al. Clin Exp Rheumatol 2014, Mariette et al. Arthritis `Rheum 2004,`Norheim et al. PlosOne 2012, Devauchelle-Pense et al. Ann Intern Med 2014, De Vita et al. Rheumatology 2015, Chevallier et al Ann Rheum Dis 2020, Sankar et al. Arthritis Rheum 2004, Baer et al. Ann Rheum Dis 2021, Bowman et al. Lancet 2022, Steinfeld et al. Arthritis Rheumatol 2018, Gottenberg et al. Arthritis Rheumatol 2018, Shao et al.Scad J rheumatol 2012, St Clair et al. Rheumatol 2021, Juarez et al. Rheumatology 2021

Sjögren's Disease

Inefficacy of Biologic Agents-Why?

- Disease course: slowly progressive and chronic rahter than relapsing-remmiting
- Short observation time for most clinical trials
- Phenotypic diversity
- Undetermined key pathogenetic mechanisms





Goules et al Clin Exp Rheumatol 2018

NECESSITY consortium minutes 2021

Tarn et al. Lancet Rheumatol 2019

Sjögren's Disease

Management-End Points of Clinical Trials

CRESS

Item	Measurement	Definition of response
Systemic disease activity	ClinESSDAI	Score <5 (low disease activity)
Patient-reported symptoms	ESSPRI	Decrease of ≥1 point or ≥15% from baseline
Tear gland*	Schirmer/OSS**	If abnormal score at baseline: • Or increase of ≥5 mm in Schirmer • Decrease of ≥2 points in OSS Or if both normal at baseline: • No change to abnormal in Schirmer and OSS
Salivary gland*	UWS/SGUS	• Increase of ≥25% or if score is 0 at baseline any increase in UWS • Or decrease of ≥25% in total Hocevar score
Serological	RF/IgG	• Decrease of ≥25% in RF • Or decrease of ≥10% in IgG
Total CRESS responder		Response on ≥3 items of 5

*CRESS can also be used without OSS and SGUS if these tests are not available
**Mean of both eyes
Abbreviations: ClinESSDAI: Clinical EULAR Sjögren's syndrome disease activity index; ESSPRI: EULAR Sjögren's syndrome patient reported index; OSS: Ocular Staining Score; UWS: unstimulated whole saliva; SGUS: salivary gland ultrasonography; RF: rheumatoid factor; IgG: Immunoglobulin G

STAR

Domain	Point	Definition of response
Systemic activity	3	Decrease of ≥3 in clinESSDAI.
Patient-reported outcome	3	Decrease of ≥1 point or ≥15% in ESSPRI.
Lachrymal gland function (assessed by Schirmer's test or ocular staining score)	1	Schirmer's test: If abnormal score at baseline: increase ≥5 mm from baseline. If normal score at baseline: no change to abnormal. *Or* Ocular staining score: If abnormal score at baseline: decrease of ≥2 points from baseline. If normal score at baseline: no change to abnormal.
Salivary gland function (assessed by unstimulated whole salivary flow or ultrasound)	1	Unstimulated whole salivary flow: If score is >0 at baseline: increase of ≥25% from baseline. If score is 0 at baseline: any increase from baseline. *Or* Ultrasound: Decrease of ≥25% in total Hocevar score from baseline.
Biological (assessed by serum IgG or RF level)	1	Serum IgG level: decrease of ≥10%. *Or* RF level: decrease of ≥25%.
Candidate STAR responder		≥5 points

Arend S et al. Arthritis Rheumatol 2020 (suppl 10)
Seror et al et al. Ann Rheum Dis 2022
Arend S et al. Lancet `Rheumatol 2019

Sjögren's Disease
Management-Cases

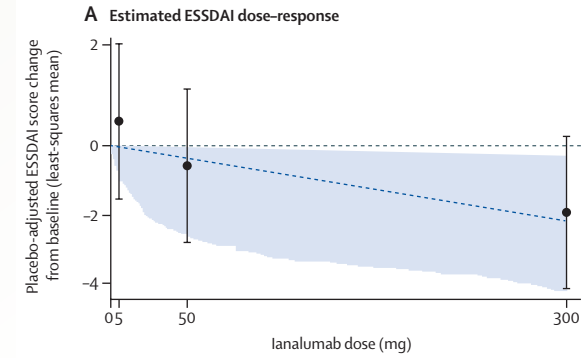
- Case 1 (oral and eye dryness)
  - **Local treatments**
- Case 2 (oral and eye dryness, interstitial nephritis/dRTA, primary biliary cholngitis, Hashimoto-extraglandular peri-epithelial manifestations)
  - **Local treatments**
  - **Ursodeoxocholic acid (UDCA): 250mg x3**
  - **Baking soda: ½ teaspoon x 2-3 (27mEq/each) ± oral potassium (goal>22mEq/L)**
- Case 3 (peristent parotid swelling, purpura, lower extremities edema/glomerulopathy—Cryoglobulinemic vasculits)
  - **Work up for lymphoma**
  - **No lymphoma or limited MALT: 0.5mg/kg GC + Rituximab**
  - **Dissiminated MALT: Rituximab + bendamustine**

Sjögren's Disease

Management-What is next?

Ianalumab

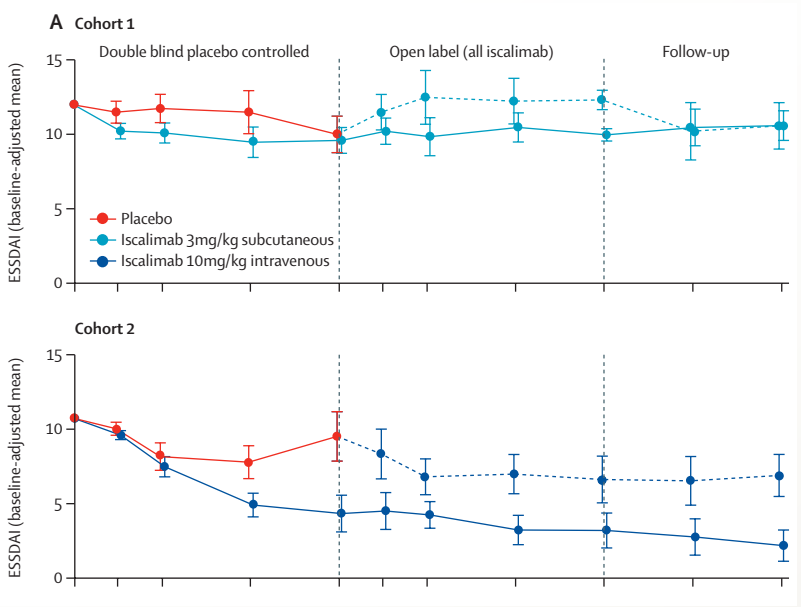
- 190 pSS→1:1:1:1 for placebo vs sc inalumab every 4 weeks for 24 weeks
- ΔESSDAI from baseline at week 24



- No difference regarding ESSPRI but in stimulated salivary flow

Iscalimab

- Cohort 1 (sc): 8 ISC vs 4 PB → W 0,2,4,8
- Cohort 2 (IV): 21 ISC vs 11 PB → W 0,2,4,8
- ΔESSDAI from baseline at week 12



- No diference regarding ESSPRI, unstimulsted salivary flow or administration route

Bowman et al. Lancet 2022

Fisher et al. Lancet Rheumatol 2020

Sjögren's Disease
Management

Concluding Remarks

- No effective therapies for overall systemic disease activity and patients' reported symptoms
- Predominaltly organ based treatment approach
- Effective trement modalities for cryoglobulinemic vasculitic manifestations targeting the B cell component
- Treatment strategy beased on tisuue/organ compartmentalization (precision medicine)

Thank you for your attention