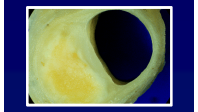




Pathogenesis of Sjogren's disease and therapeutic appoaches

Pr Alain Saraux

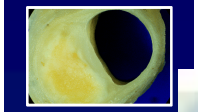
CHU de la Cavale Blanche

29609 Brest Cedex

Breast

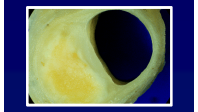
Brest

The town of the international festival of laughter



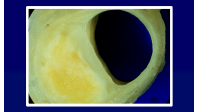
Persons who don’t cry when they **laugh**

Primary Sjogren’s syndrom (pSS)



Plan

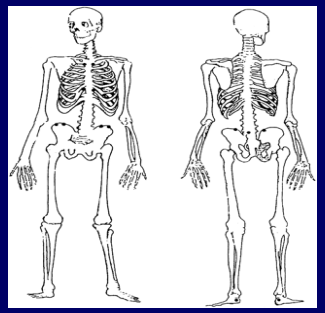
- Sjogren’s syndrom
- Current treatment
- Physiopathology
- Future treatment

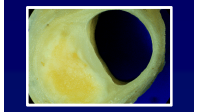


Modes of onset

	Dryness	Parotid gland enlargement	Fatigue /Pain	Extra-glandular signs

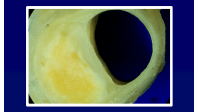




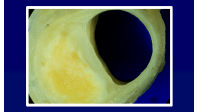



Diagnosis

Main differential Diagnosis		Positive Diagnosis
Dry syndrome	-Drugs	- Dry Mouth - Dry eye - Salivary Flow - Schirmer‘s test - Rose Bengal ou Lissamine green test - Break up test - Ocular staining score - Salivary gland biopsy - Anti-SSA/Ro and/or anti-SSB/La +/- Salivary gland ultrasonography
Parotid gland enlargement	-Lymphoma -Sarcoïdosis -Hyper IgG4 syndrome	
Fatigue /Pain	-Fibromyalgia -other connective tissue disease	
Extra-articular signs	-Hepatitis C -VIH -GVH	

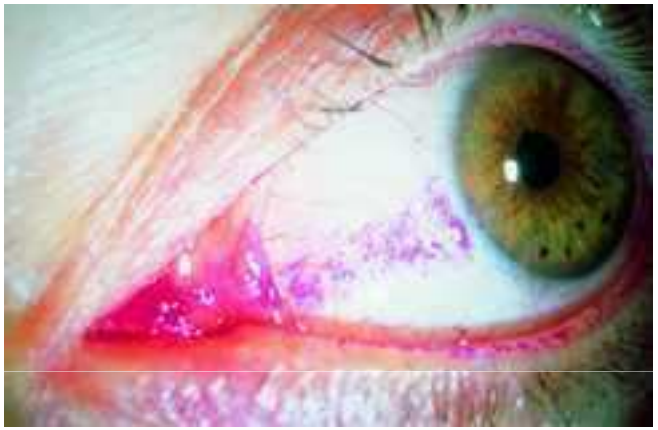


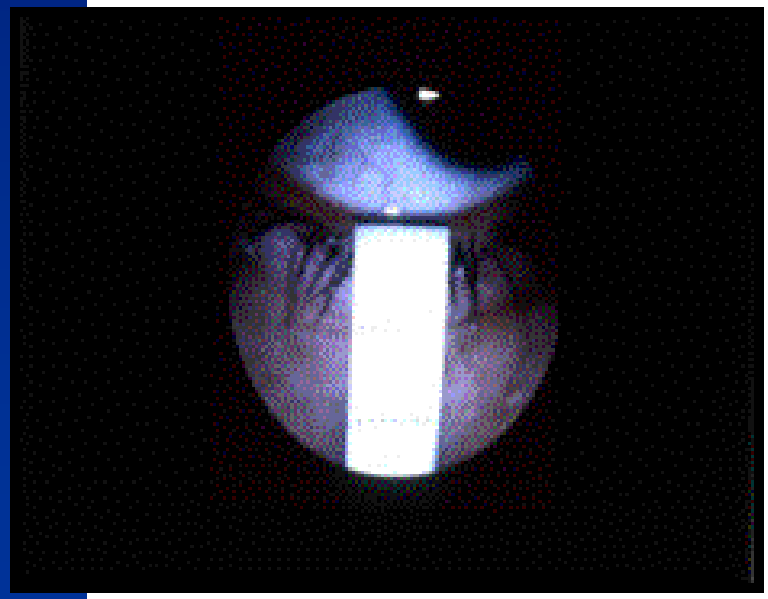
Salivary flow

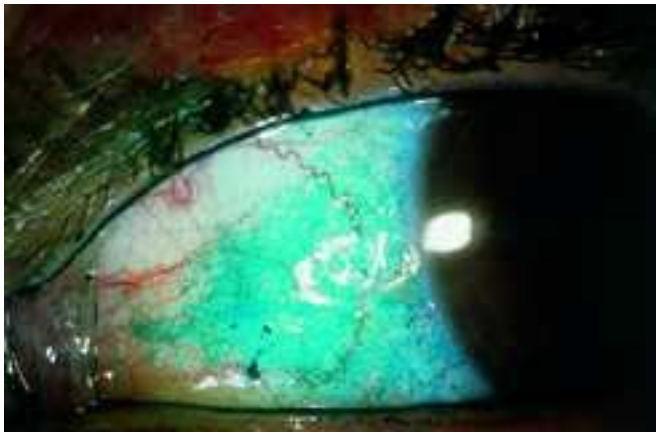


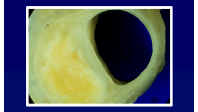
Schirmer, BUT, VB and OSS

- Schirmer: Calibrated strips of filter paper placed within eyelid
- B.U.T (Beak up test): fluorescéine
- Rose Bengale or vert Lissamine: Van Bijsterveld or OSS (ocular staining score)

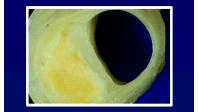




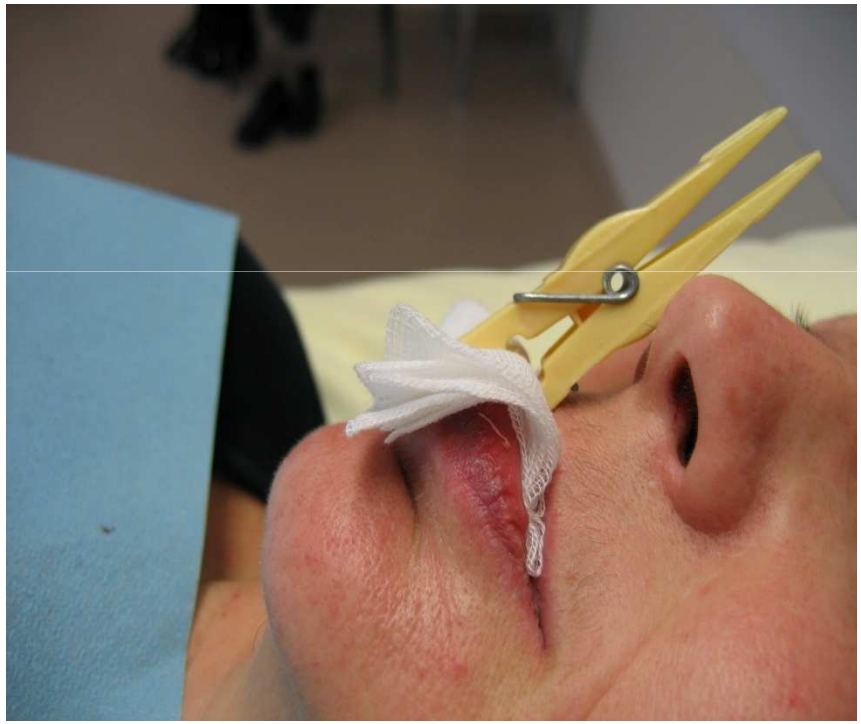




Salivary Gland labial Biopsy

Salivary Gland labial Biopsy

Costa *et al. Arthritis Research & Therapy* (2016) 18:21
DOI 10.1186/s13075-016-0924-2

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

B-cell and T-cell quantification in minor salivary glands in primary Sjögren's syndrome: development and validation of a pixel-based digital procedure

Sebastian Costa[1*], Sacha Schutz[2], Divi Cornec[3], Arnaud Uguen[1], Isabelle Quintin-Roué[1], Agnès Lesourd[4], Jean-Marie Berthelot[5], Eric Hachulla[6], Pierre-Yves Hatron[6], Vincent Goeb[7], Olivier Vittecoq[8], Jacques Olivier Pers[9], Pascale Marcorelles[10], Alain Saraux[11] and Valérie Devauchelle-Pensec[11]

Conclusion: The digital procedure proved accurate compared to the reference standard, producing reliable results for whole tissue sections.

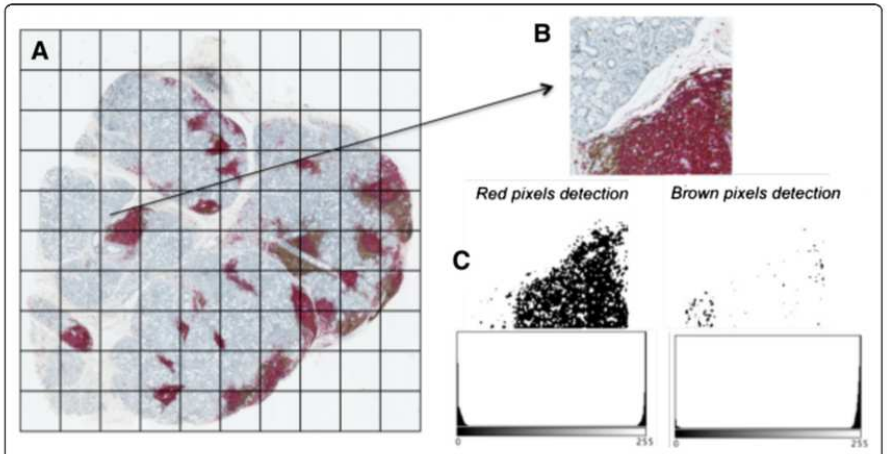


Fig. 1 The digital pixel counting procedure. **a** A minor salivary gland biopsy section on a standard glass slide was scanned using the NanoZoomer HT Scan system. **b** The NDPI file thus obtained was divided into several JPEG format files, which restored the original image if reassembled. The JPEG format files were managed by the algorythm (source code, available on https://github.com/dridk/bgsa-ndpi). **c** The signal in a given pixel was partitioned using a linear unmixing algorithm with simple red/green/blue imagery

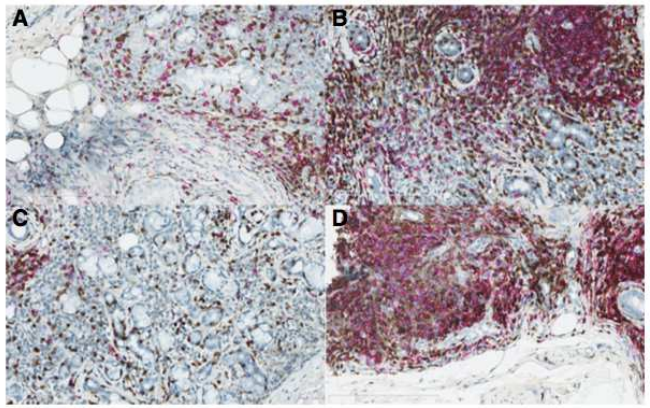
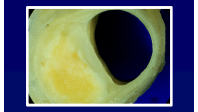
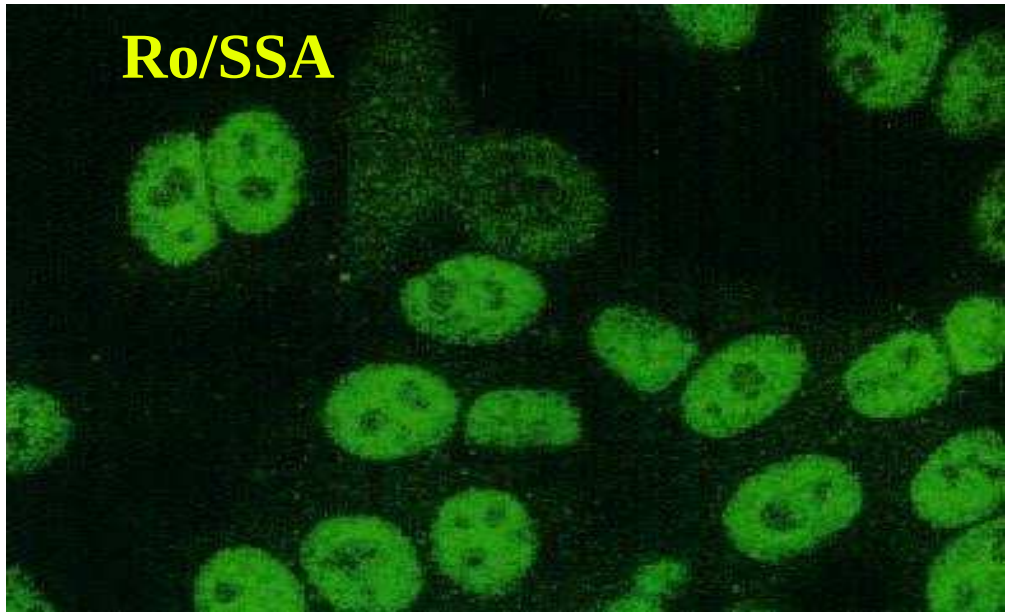
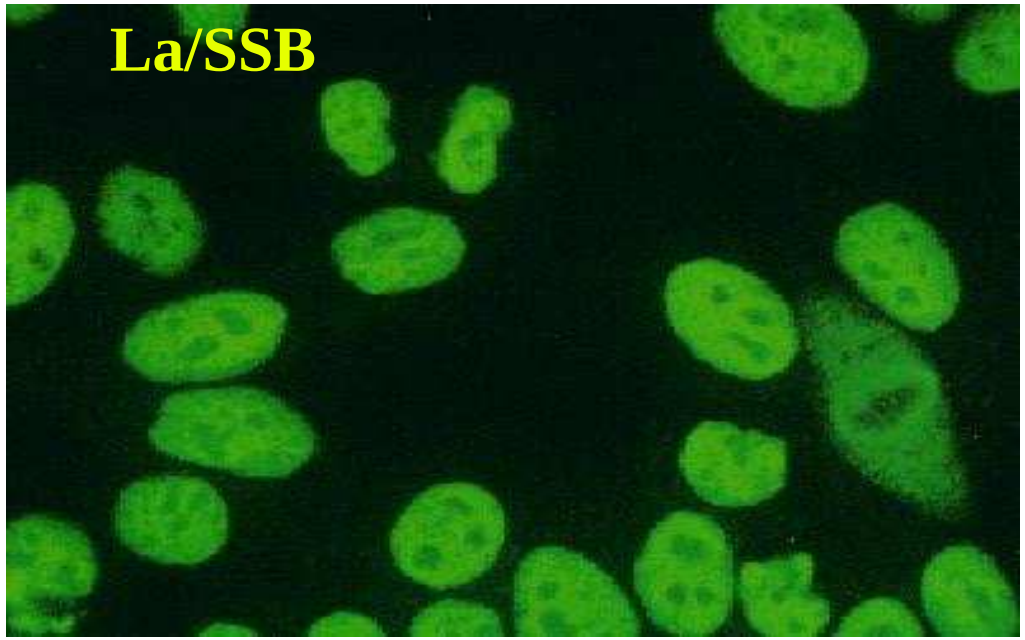


Fig. 2 Micrographs of four JPEG format images showing the manual-count mask used by the ImageJ Cell counter. Stained B cells (in *red*) are marked with a dark blue dot and stained T cells (in *brown*) with a light blue dot. **a** First JPEG format image. Manual B-/T-cell counts: 135/361 (investigator 1) and 159/406 (investigator 2). Digital B-/T-cell count: 120/423. **b** Second JPEG format image. Manual B-/T-cell counts: 689/1067 (investigator 1) and 751/1089 (investigator 2). Digital B-/T-cell count: 532/1014. **c** Third JPEG-format image. Manual B-/T-cell count: 41/356 (investigator 1) and 50/426 (investigator 2). Digital B-/T-cell count: 36/410. **d** Fourth JPEG format image. Manual B-/T-cell counts: 469/860 (investigator 1) and 448/841 (investigator 2). Digital B-/T-cell count: 599/820




Ro/SSA


La/SSB

Level of agreement between 2002 American–European Consensus Group and 2012 American College of Rheumatology classification criteria for Sjögren's syndrome and reasons for discrepancies

Divi Cornec[1,2], Alain Saraux[1,2], Béatrice Cochener[3], Jacques-Olivier Pers[2,4], Sandrine Jousse-Joulin[1,2], Yves Renaudineau[2,5], Thierry Marhadour[1] and Valérie Devauchelle-Pensec[1,2,6*]

Table 1 Pragmatic AECG [1] and ACR [2] classification criteria for Sjögren's syndrome

	Pragmatic 2002 AECG criteria	2012 ACR criteria
Items	1. Ocular dryness symptoms	1. Positive anti-SSA or anti-SSB antibodies or positive rheumatoid factor plus ANA ≥1:320
	2. Oral dryness symptoms	2. Focus score ≥1 focus/4 mm^2 on minor salivary gland biopsy
	3. Ocular signs: Schirmer's test ≤5 mm/5 minutes	3. Keratoconjunctivitis sicca with ocular staining score ≥3
	4. Focus score ≥1 focus/4 mm^2 on minor salivary gland biopsy	
	5. Salivary gland involvement: unstimulated whole salivary flow ≤0.1 ml/minute	
	6. Positive anti-SSA or anti-SSB antibodies	
Rules for classification	Presence of any four of the six items with at least item 4 or 6, or presence of any three of the four objective items (items 3, 4, 5 and 6)	In a patient with suspected Sjögren's syndrome, any two of the three items

There was two distincts criteria published by ACR/EULAR in 2002 and ACR ten years later

Level of agreement between 2002 American–European Consensus Group and 2012 American College of Rheumatology classification criteria for Sjögren's syndrome and reasons for discrepancies

Divi Cornec[1,2], Alain Saraux[1,2], Béatrice Cochener[3], Jacques-Olivier Pers[2,4], Sandrine Jousse-Joulin[1,2], Yves Renaudineau[2,5], Thierry Marhadour[1] and Valérie Devauchelle-Pensec[1,2,6*]

Both sets	ACR set only	AECG set only	Neither set
(*n* = 27)	(*n* = 8)	(*n* = 15)	(*n* = 55)

With discordance between them

Justiying new criteria

Cornec *et al. Arthritis Research & Therapy* 2014, **16**:R74

ACR/EULAR

The principle is based on five objective items: total score ≥ 4

Item	Weight / Score
LSG with FLS and FS ≥ 1[3]	3
Anti-SSA (Ro) +	3
OSS ≥ 5 (or VB ≥ 4) on at least one eye[4]	1
Schirmer ≤ 5 mm/5min on at least one eye	1
UWS[5] flow rate ≤ 0.1 ml/min	1

Shiboski C, submitted

ARTHRITIS & RHEUMATISM
Vol. 65, No. 1, January 2013, pp 216–225
DOI 10.1002/art.37698

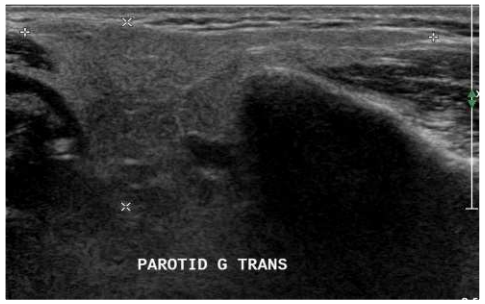
Contribution of Salivary Gland Ultrasonography to the Diagnosis of Sjögren's Syndrome

Toward New Diagnostic Criteria?

Divi Cornec,[1] Sandrine Jousse-Joulin,[1] Jacques-Olivier Pers,[1] Thierry Marhadour,[1] Béatrice Cochener,[2] Sylvie Boisramé-Gastrin,[3] Emmanuel Nowak,[4] Pierre Youinou,[1] Alain Saraux,[1] and Valérie Devauchelle-Pensec[1]

- Parotid: transversal plane





- Parotid: longitudinal plane



- Submandibular



Table 3. Echostructure grade assessing parenchymal inhomogeneity of the major salivary glands in patients with and those without primary SS*

US grade	Patients with primary SS (n = 78)	Patients without primary SS (n = 80)
0	22	62
1	7	14
2	7	3
3	25	1
4	17	0

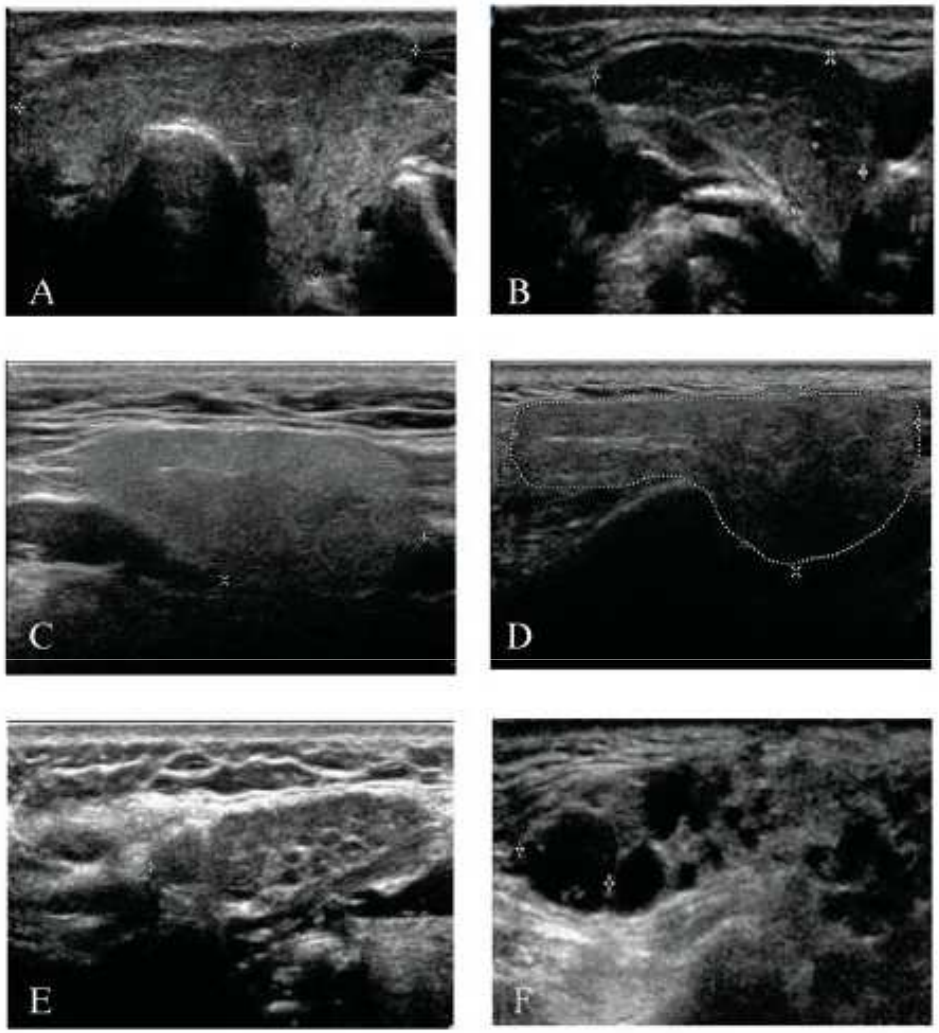


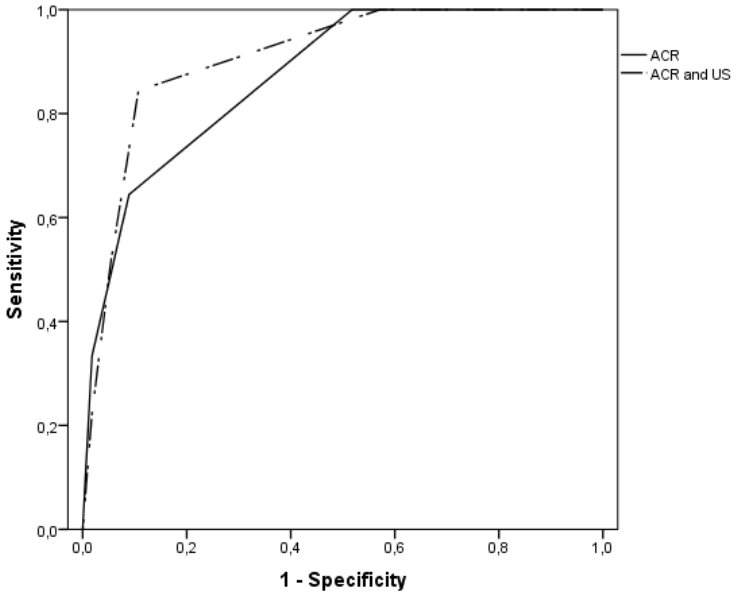
Figure 1. A–F, Representative images illustrating salivary gland echostructure grading. **A,** Normal parotid gland (grade 0). **B,** Normal submandibular gland (grade 0). **C,** Grade 1 submandibular gland, with hypoechogenic fiber. **D,** Grade 2 parotid gland, with multiple hypoechogenic areas measuring <2 mm and hyperechogenic bands. **E,** Grade 3 submandibular gland, with multiple hypoechogenic areas measuring 2–6 mm and hyperechogenic bands. **F,** Grade 4 parotid gland, with multiple hypoechogenic areas measuring >6 mm. **G** and **H,** Blood flow to the parotid gland, as assessed by Doppler waveform analysis of the transverse facial artery, before (**G**) and during (**H**) stimulation with lemon juice.

RHEUMATOLOGY 273, 294

Concise report doi:10.1093/rheumatology/keu037

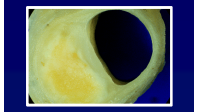
Salivary gland ultrasonography improves the diagnostic performance of the 2012 American College of Rheumatology classification criteria for Sjögren's syndrome

Divi Cornec[1,2], Sandrine Jousse-Joulin[1,2], Thierry Marhadour[1], Jacques-Olivier Pers[2,3], Sylvie Boisramé-Gastrin[3], Yves Renaudineau[2,4], Alain Saraux[1,2] and Valérie Devauchelle-Pensec[1,2]



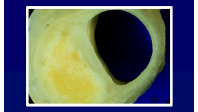
	Se	Sp	PPV	NPV
ACR criteria	64.4	91.1	85.3	76.1
ACR criteria + SGUS	84.4	89.3	86.7	87.7

US clearly improve previous criteria.



Assessment

B lymphocyte Activity	Criteria for poor prognosis	Extra-glandular signs ESSDAI	Dryness, Pain, Fatigue ESSPRI
-Rheumatoid Factors -Ac-anti-SS-A, SS-B -ß2-microglobulin- -Electrophoresis of plasma proteins -Complement -Cryoglobulinemia	-Parotidomegaly -polyadenopathy -Purpura -Vasculitis -Anemia -Lymphopenia -Low C4 -Cryoglobulinemia	-Pulmonary -Skin -parotid -Neurological -Articular -Pancreatic -Renal -cytopenia -Muscle -Lymph	-Pain VAS, tireness, dryness and pain -Stomatological Consultation -ophtalmologic Consultation



Validation of EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI)

Raphaèle Seror,[1,2] Elke Theander,[3] Johan G Brun,[4] Manel Ramos-Casals,[5] Valeria Valim,[6] Thomas Dörner,[7] Hendrika Bootsma,[8] Athanasios Tzioufas,[9] Roser Solans-Laqué,[10] Thomas Mandl,[3] Jacques-Eric Gottenberg,[11] Eric Hachulla,[12] Kathy L Sivils,[13] Wan-Fai Ng,[14] Anne-Laure Fauchais,[15] Stefano Bombardieri,[16] Guido Valesini,[17] Elena Bartoloni,[18] Alain Saraux,[19] Matija Tomsic,[20] Takayuki Sumida,[21] Susumu Nishiyama,[22] Roberto Caporali,[23] Aike A Kruize,[24] Cristina Vollenweider,[25] Philippe Ravaud,[2] Claudio Vitali,[26] Xavier Mariette,[1] Simon J Bowman,[27] on behalf of the EULAR Sjögren's Task Force

Table 1 The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI): domain and item definitions and scores

Domain	Activity level	Description
Constitutional *Exclusion of fever of infectious origin and voluntary weight loss*	No=0 Low=3 Moderate=6	Absence of the following symptoms Mild or intermittent fever (37.5°–38.5°C)/night sweats and/or involuntary weight loss of 5–10% of body weight Severe fever (>38.5°C) / night sweats and/or involuntary weight loss of >10% of body weight
Lymphadenopathy *Exclusion of infection*	No=0 Low=4 Moderate=8 High=12	Absence of the following features Lymphadenopathy ≥1 cm in any nodal region or ≥2 cm in inguinal region Lymphadenopathy ≥2 cm in any nodal region or ≥3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging) Current malignant B-cell proliferative disorder*
Glandular *Exclusion of stone or infection*	No=0 Low=2 Moderate=4	Absence of glandular swelling Small glandular swelling with enlarged parotid (≤3 cm), or limited submandibular or lachrymal swelling Major glandular swelling with enlarged parotid (>3 cm), or important submandibular or lachrymal swelling
Articular *Exclusion of osteoarthritis*	No=0 Low=2 Moderate=4 High=6	Absence of currently active articular involvement Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min) 1–5 (of 28 total count) synovitis ≥6 (of 28 total count) synovitis

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

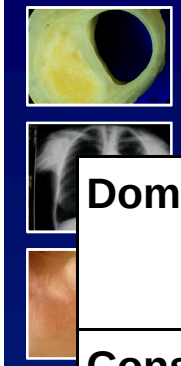
2) How severe has your fatigue been during the last 2 weeks ?

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

Seror et al, ARD 2014



ESSDAI

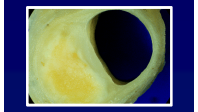
Domains	Weights	No Activity 0	Low Activity 1	Moderate Activity 2	High Activity 3
Constitutional symptoms	3	○	○	○	○
Lymphadenopathy	4	○	○	○	○
Glandular swelling	2	○	○	○	○
Articular	2	○	○	○	○
Cutaneous	3	○	○	○	○
Pulmonary	5	○	○	○	○
Renal	5	○	○	○	○
Muscular	6	○	○	○	○
Peripheral Nervous System	5	○	○	○	○
Central Nervous System	5	○	○	○	○
Hematological	2	○	○	○	○
Biological	1	○	○	○	○

Table 3. The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI): Domain and item definitions and weights.

Domain [Weight]	Activity level	Description
Constitutional [3] *Exclusion of fever of infectious origin and voluntary weight loss*	No = 0	Absence of the following symptoms
	Low = 1	Mild or intermittent fever (37.5°-38.5°C) / night sweats and/or involuntary weight loss of 5 to 10% of body weight
	Moderate = 2	Severe fever (>38.5°C) / night sweats and/or involuntary weight loss of >10% of body weight
Lymphadenopathy [4] *Exclusion of infection*	No = 0	Absence of the following features
	Low = 1	Lymphadenopathy ≥ 1 cm in any nodal region or ≥ 2 cm in inguinal region
	Moderate = 2	Lymphadenopathy ≥ 2 cm in any nodal region or ≥ 3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging)
	High = 3	Current malignant B-cell proliferative disorder
Glandular [2] *Exclusion of stone or infection*	No = 0	Absence of glandular swelling
	Low =1	Small glandular swelling with enlarged parotid (≤ 3 cm), or limited submandibular or lachrymal swelling
	Moderate = 2	Major glandular swelling with enlarged parotid (> 3 cm), or important submandibular or lachrymal swelling
Articular [2] *Exclusion of osteoarthritis*	No = 0	Absence of currently active articular involvement
	Low = 1	Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min)
	Moderate = 2	1 to 5 (of 28 total count) synovitis
	High = 3	≥ 6 (of 28 total count) synovitis
Cutaneous [3] *Rate as "No activity" stable long-lasting features related to damage*	No = 0	Absence of currently active cutaneous involvement
	Low =1	Erythema multiforma
	Moderate = 2	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
	High = 3	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis
Pulmonary [5] *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 = 1	Persistent cough or 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 = 2	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 = 3	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%
Renal [5] *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/d, no hematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage
	Low = 1	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/d) and without hematuria or renal failure (GFR ≥60 ml/min)
	Moderate = 2	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/d and without hematuria or renal failure (GFR ≥60 ml/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High = 3	Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/d or hematuria or renal failure (GFR <60 ml/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinemia related renal involvement

Muscular [6] *Exclusion of weakness due to corticosteroids*	No = 0	Absence of currently active muscular involvement
	Low = 1	Mild active myositis shown by abnormal EMG or biopsy with no weakness and creatine kinase (N <CK ≤ 2N)
	Moderate = 2	Moderately active myositis proven by abnormal EMG or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N <CK ≤4N),
	High = 3	Highly active myositis shown by abnormal EMG or biopsy with weakness (deficit ≤ 3/5) or elevated creatine kinase (>4N)
PNS [5] *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 = 1	Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia
	Moderate = 2	Moderately active peripheral nervous system 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 4/5or mild ataxia), Or cranial nerve involvement of peripheral origin (except trigeminal (V) neralgia)
	High = 3	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
CNS [5] *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
	Low = 1	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 = 3	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit.
Hematological [2] *For anemia, neutropenia, and thrombopenia, only auto-immune cytopenia must be considered* *Exclusion of vitamin or iron deficiency, drug-induced cytopenia*	No = 0	Absence of auto-immune cytopenia
	Low = 1	Cytopenia of auto-immune origin with neutropenia (1000 < neutrophils < 1500/mm3), and/or anemia (10 < hemoglobin < 12 g/dl), and /or thrombocytopenia (100,000 < platelets < 150,000/mm3) Or lymphopenia (500 < lymphocytes < 1000/mm3)
	Moderate = 2	Cytopenia of auto-immune origin with neutropenia (500 ≤ neutrophils ≤ 1000/mm3), and/or anemia (8 ≤ hemoglobin ≤ 10 g/dl), and/or thrombocytopenia (50,000 ≤ platelets ≤ 100,000/mm3) Or lymphopenia (≤500/mm3)
	High = 3	Cytopenia of auto-immune origin with neutropenia (neutrophils < 500/mm3), and/or or anemia (hemoglobin < 8 g/dl) and/or thrombocytopenia (platelets <50,000/mm3)
Biological [1]	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)

CIDP= chronic inflammatory demyelinating polyneuropathy; CK= creatine kinase; CNS= central nervous system; DLCO= diffusing CO capacity; EMG= electromyogram; FVC= forced vital capacity; GFR= glomerular filtration rate; Hb= hemoglobin; HRCT= high-resolution computed tomography; IgG= immunoglobulin G; NCS= nerve conduction studies; NHYA= New York heart association classification; Plt= platelet; PNS=peripheral nervous system;



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

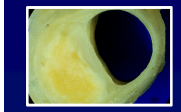
2) How severe has your fatigue been during the last 2 weeks ?

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

Seror et al., ARD 2009

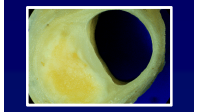


Treatment of Primary Sjögren's Syndrome

therapeutic armamentarium available for pSS

- Avoid drugs responsible of dryness
- **Topical medication**
- **Synthetic Systemic medication**
  - **secretagogues and electrostimulation**
  - **DMARDs**
- **Biological Systemic medication**

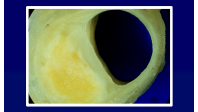
Review double blind studies



Controlled therapeutic trials of secretagogues and electrostimulation in Sjögren's syndrome

Author	Inclusion criteria	Treatment	N	Primary endpoint	Significance
27	1993 ACR criteria	Pilocarpine [5 mg/6 h]	44	Increased saliva production at wk 6 and 12 and global improvement of dry mouth (VAS)	Yes
25	1993 ECCC criteria	Pilocarpine [5 mg/6 h or 2.5 mg/6 h]	373	Improvement of dry mouth and dry eyes (VAS) at wk 6 and 12 and increased salivary flow	Yes
26	2002 AECG criteria	Pilocarpine [5 mg/6 h wk 0-6 and 7.5 mg/6 h wk 6-12]	256	Improvement of dry mouth and dry eyes at wk 12	Yes
39	2002 AECG criteria	Pilocarpine [5 mg/12 h]	85	Improvement of ocular symptoms at wk 12	Yes
29	2002 AECG criteria and associated lachrymal and salivary gland dysfunction	Cevimeline [30 mg/8 h, 60 mg/8 h]	75	Improvement of dry mouth and dry eyes (VAS) at wk 6	Yes

Nature Reviews Rheumatology 2016 in press

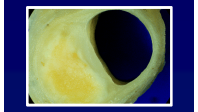


Controlled therapeutic trials of secretagogues and electrostimulation in Sjögren's syndrome

30	2002 AECG criteria	Cevimeline [30 mg/8 h]	44 Improvement of dry mouth and whole salivary flow rate	Yes for dry mouth improvement
132	Confirmed or suspected SS based on the Japanese Ministry of Health and Welfare criteria	Cevimeline [20 mg/8 h or 30 mg/8 h]	60 Improvement of subjective symptoms of dry eyes at wk 4	Yes
28	2002 AECG criteria	Cevimeline [15 mg/8 h or 30 mg/8 h]	197 Improvement of dry eyes, dry mouth, and overall dryness at wk 3, 6, 9 and 12	Yes
22	Patients with xerostomia and focal chronic sialadenitis	Electrostimulation	29 Improvement of whole salivary flow at wk 4	No
23	Patients with secondary SS complaining of dry month	Electrostimulation	77 Increase in saliva production at wk 4	Yes
24	Patients with xerostomia, including 66 meeting AECG criteria for SS	Electrostimulation	114 Improvement in xerostomia severity at wk 12	Yes

Controlled therapeutic trials of synthetic treatments in primary Sjögren's syndrome

Author	Treatment	N	Primary endpoint	Significance
43	Hydroxychloroquine	120	30% improvement in ≥2 of 3 VAS scores	No
46	Dehydroepiandrosterone (DHEA)	107	MFI-20	No
44	Dehydroepiandrosterone (DHEA)	60	Fatigue	No
45	Omega 6	90	VAS fatigue score	No
133	Azathioprine	25	Clinical and biological efficacy	No
47	Hydroxychloroquine	19	Clinical and biological efficacy	No, except on hypergammaglobulinaemia, IgM and ESR
134	Cyclosporine A	10	Clinical and biological efficacy	No, except subjective xerostomia



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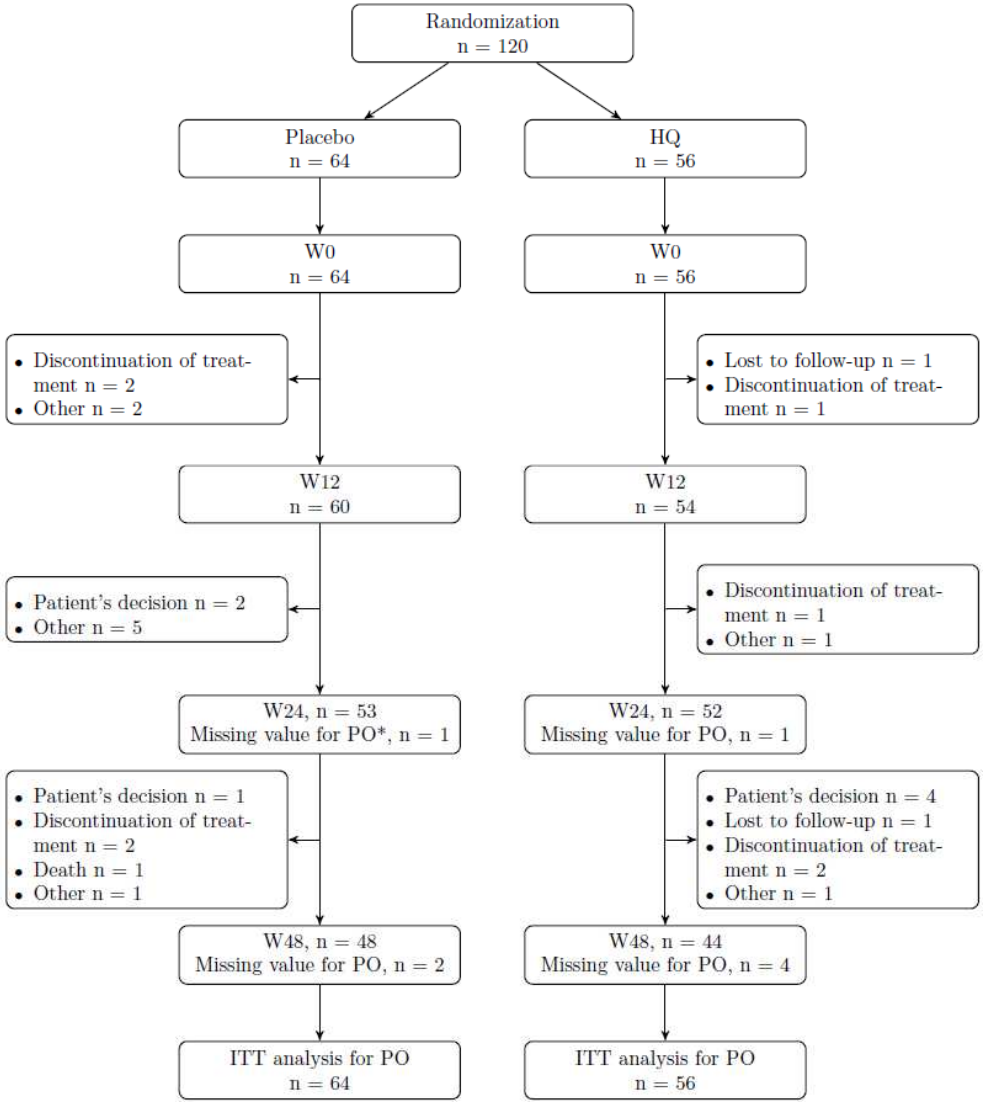
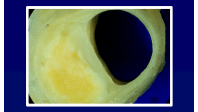


Gottenberg et al. JAMA. 2014 16;312(3):249-58.



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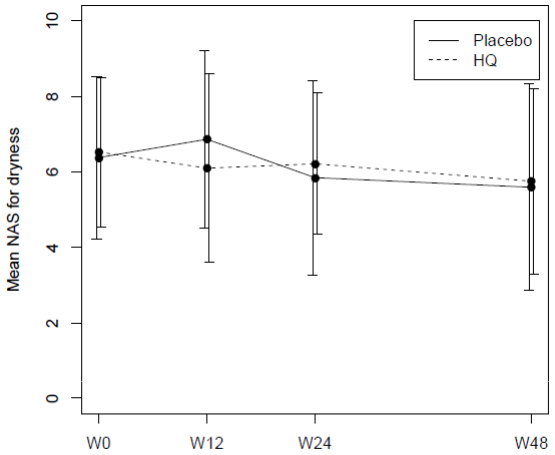

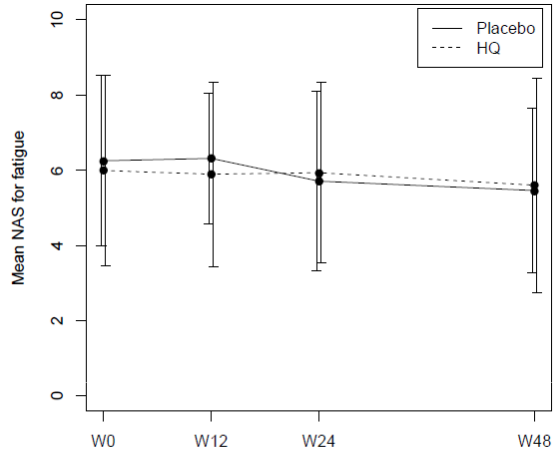

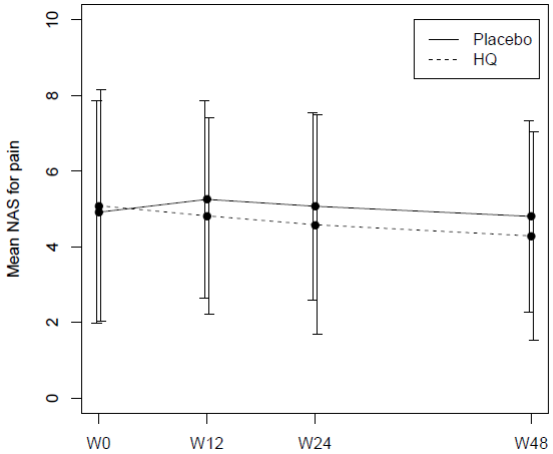

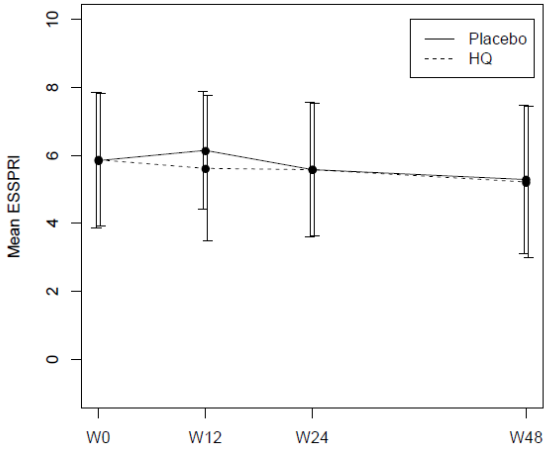

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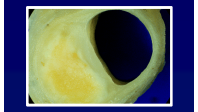


Treatment of Primary Sjögren's Syndrome

Oxford Centre for Evidence-based Medicine-levels of Evidence www.cebm.net

Grade A : Consistent level 1 studies;

Grade B: Consistent level 2 or 3 studies or extrapolations from level 1 studies;

Grade C: Level 4 studies or extrapolations from level 2 or 3 studies;

Grade D: Level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

Level 1 to 5

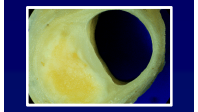
1a: Systematic review of RCTs; 1b: individual randomized trial; 1c: all or none case-series

2a: Systematic review of cohort studies; 2b: individual cohort study; 2c: "outcomes" research

3a: Systematic review of case-control studies; 3b: Individual case-control study

4: Case-series

5: Expert opinion



Treatment of Primary Sjögren's Syndrome

Dryness

Dry mouth
Topical fluoride (A)
Gustatory and masticatory stimulation (C)
Pharmaceutical agents, Chlorhexidine varnish, gel or rinse, Electrostimulation (C)
Secretagogues (pilocarpine and cevimeline) (A)
Dry eyes
Education and environment modification, elimination of offending systemic manifestation, artificial tears, gel ointments (A)
Local cyclosporine (B)
Pulse steroids (C)
Punctal plugs (C)
Secretagogues (pilocarpine and cevimeline) (A)
Meibomian disease
Artificial tears with lipid complements, warm compress and massage, topical azithromycin, liposomal spray, oral doxycycline, expression of meibomian glands, systemic anti-inflammatory medication or eyelid surgery (C)

Parotid enlargement

Acute bilateral severe parotid swelling:
Look for lymphoma
Otherwise, steroids (B)

Chronic bilateral parotid swelling:
Look for lymphoma
Surgery (rare) (D)

Acute unilateral severe parotid swelling:
Look for infection (ultrasound): antibiotic (covering anaerobes) (D)
Look for infection or calcification in the ducts
Otherwise, NSAID or steroid<20 mg and <1 month (D)

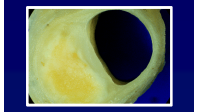
Extra-glandular signs

None-life-threatening:
Exercise for fatigue (C), NSAID (C), Hydroxychloroquine (C), Imunosuppressant **(**Leflunomide; Sulfasalazine, Azathioprine, Cyclosporine, Cyclophosphamide) and/or steroids should be considered according to activity (see Table 4)

Life threatening:
Methylprednisolone pulses and plasma exchange if cryoglobulinaemia (C)

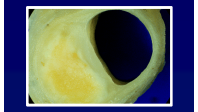
In patients with cryoglobulinaemia and vasculitis, rituximab should be considered (C)

Saraux et al. Nature Reviews Rheumatology 2016 in press



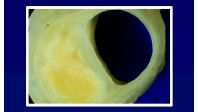
Treatment of Primary Sjögren's Syndrome

Domain	Low activity
Constitutional	Advice about exercise if fatigue (B)
Lymphadenopathy	Abstention (D)
Glandular	Abstention (D) NSAID (D)
Arthralgia or arthritis	Treatment as chronic pain, NSAID (C)
Cutaneous	Abstention (D) Cutaneous topical agents (C)
Respiratory	Treatment of sicca, inhaled steroids or β2 adrenergic agonists (D)
Renal	Abstention and careful monitoring (D)
Muscle	Abstention (D)
Peripheral nervous	Treatment as chronic pain (D)
Central nervous	NA (D)
Haematological	Abstention (D)
Biological	Abstention (D)



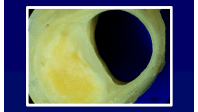
Treatment of Primary Sjögren's Syndrome

Domain	Moderate activity
Constitutional	Hydroxychloroquine (C) Short-term oral steroids (C)
Lymphadenopathy	Abstention (D)
Glandular	Abstention (D)
Arthralgia or arthritis	Hydroxychloroquine (C) Methotrexate (D) Short-term oral or intraarticular steroids if arthritis (C)
Cutaneous	Abstention (D) Cutaneous topical agents (C) Hydroxychloroquine (C)
Respiratory	Careful monitoring or oral steroids (D)
Renal	Glomerular disease: Steroids (D) Tubulopathy: K^+ and HCO_3 if necessary (D)
Muscle	steroids (D)
Peripheral nervous	Oral or IV steroids or IVIg or both (D)
Central nervous	Oral or IV steroids (D)
Haematological	Oral steroids (C) Hydroxychloroquine (D)
Biological	Abstention (D)



Treatment of Primary Sjögren's Syndrome

Domain	High activity
Constitutional	NA
Lymphadenopathy	Treatment as lymphoma (D)
Glandular	Short-term oral steroids (D) Sialendoscopy (D) Intraductal steroids (D)
Arthralgia or arthritis	Hydroxychloroquine (C) Methotrexate (D) Second-line DMARD as in rheumatoid arthritis if arthritis (C) Oral steroids but as briefly as possible (D)
Cutaneous	Hydroxychloroquine (C) Oral steroids (C)
Respiratory	Oral or IV steroids, immunosuppressants, pirfenidone or nintedanib (C)
Renal	Glomerular disease: Steroids (C) Tubulopathy: K^+ and HCO_3 if necessary (D) Rituximab if cryoglobulinaemia (D)
Muscle	Methotrexate plus steroids (D)
Peripheral nervous	IV steroid or IVIg or immunosuppressants (D)
Central nervous	Steroids or immunosuppressants (D)
Haematological	Oral or IV steroids (D)
Biological	NA



Genetic factors

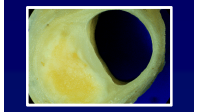
A1 B8 DR3 DQ2

HLA DRB1 03 associated to anti-SS-B + anti-SS-A

HLA DRB1 15 associated to anti-SS-A without Ac anti-SS-B.

Polymorphism of 2 genes

- IRF-5 : interferon (IFN) type 1
- STAT4: transcription factor leading to production of interferon type 2

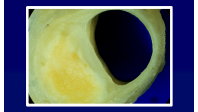


Interferon

IFN type 1 or 2 → BAFF (or BLyS) → activation of B lymphocytes:

- Analyse of transcriptoma (RNA in tissue) of mononuclear cell in blood: signature « Interferon »
- Dendritic plasmacytoid salivary gland cells → interferon
- 2 mecanisms :
  - bacterial or viral infection
  - or stimulation by immune complexes (SS-A and anticorps anti SS-A?)

Activity of cells in the gland as markers presents (HLA-DR, IL-2r (CD25))

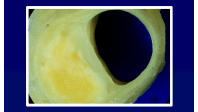


Lymphocytes

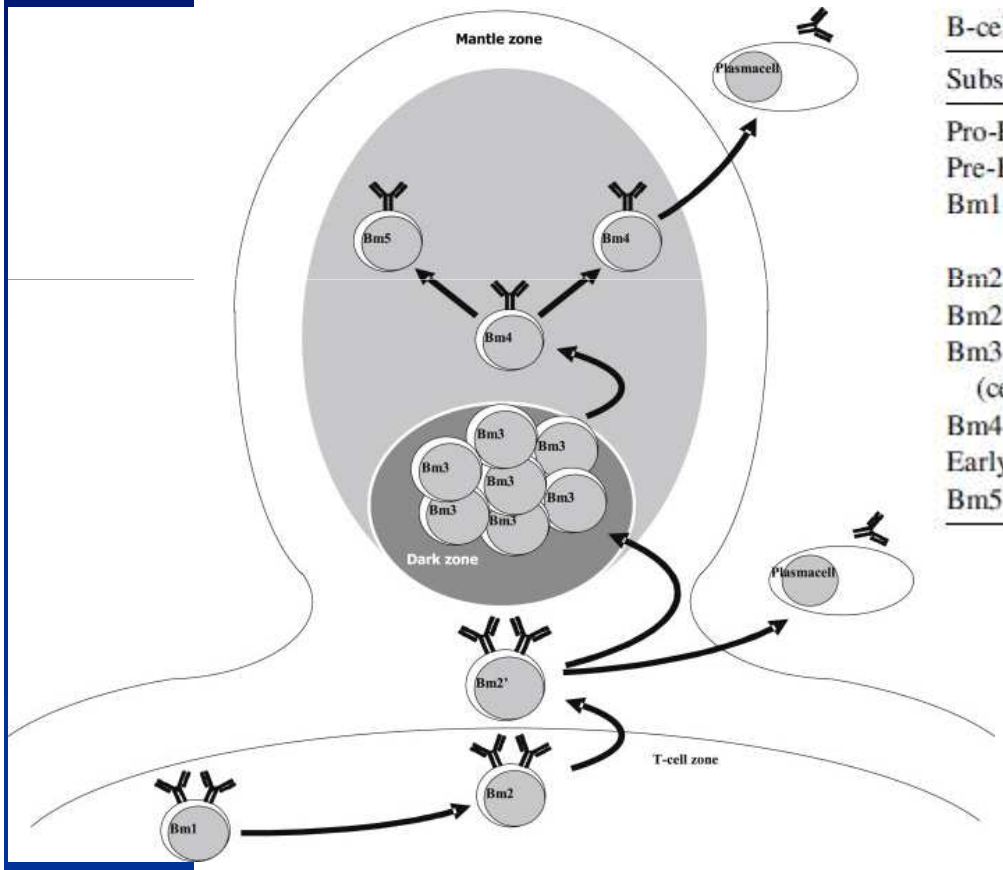
- Lymphocytic infiltration is the histological hallmark of pSS.
  - T cells contribute the vast majority of the mononuclear cells
  - 50%-70% $CD4^+$ cells
  - Macrophages, dendritic cells, and natural killer cells only about 5% to 10%.

- Nevertheless, advanced lesions contain up to 50% of B cells.

- B lymphocytes
  - Produce anti-SS-A, anti-SS-B and RF
  - Oligoclonal B cell in salivary glands, with risk of lymphoma.
  - Role of innate immunity (infection) and adaptative immunity on BAFF
  - Other cytokines such as IL-6 and IL-21 over produced
  - Activation of auto reactive B lymphocytes B



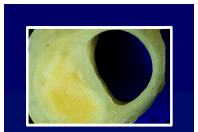
B lymphocytes

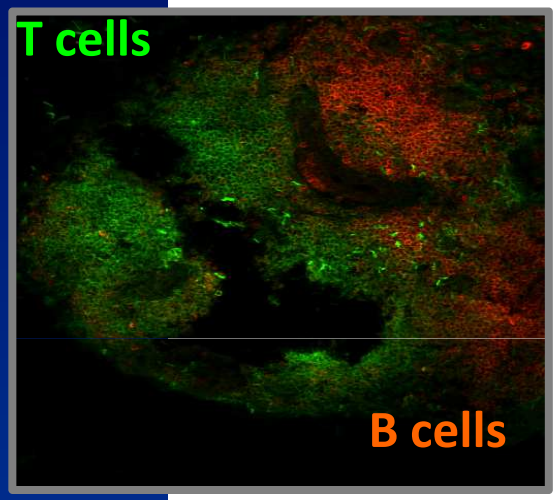


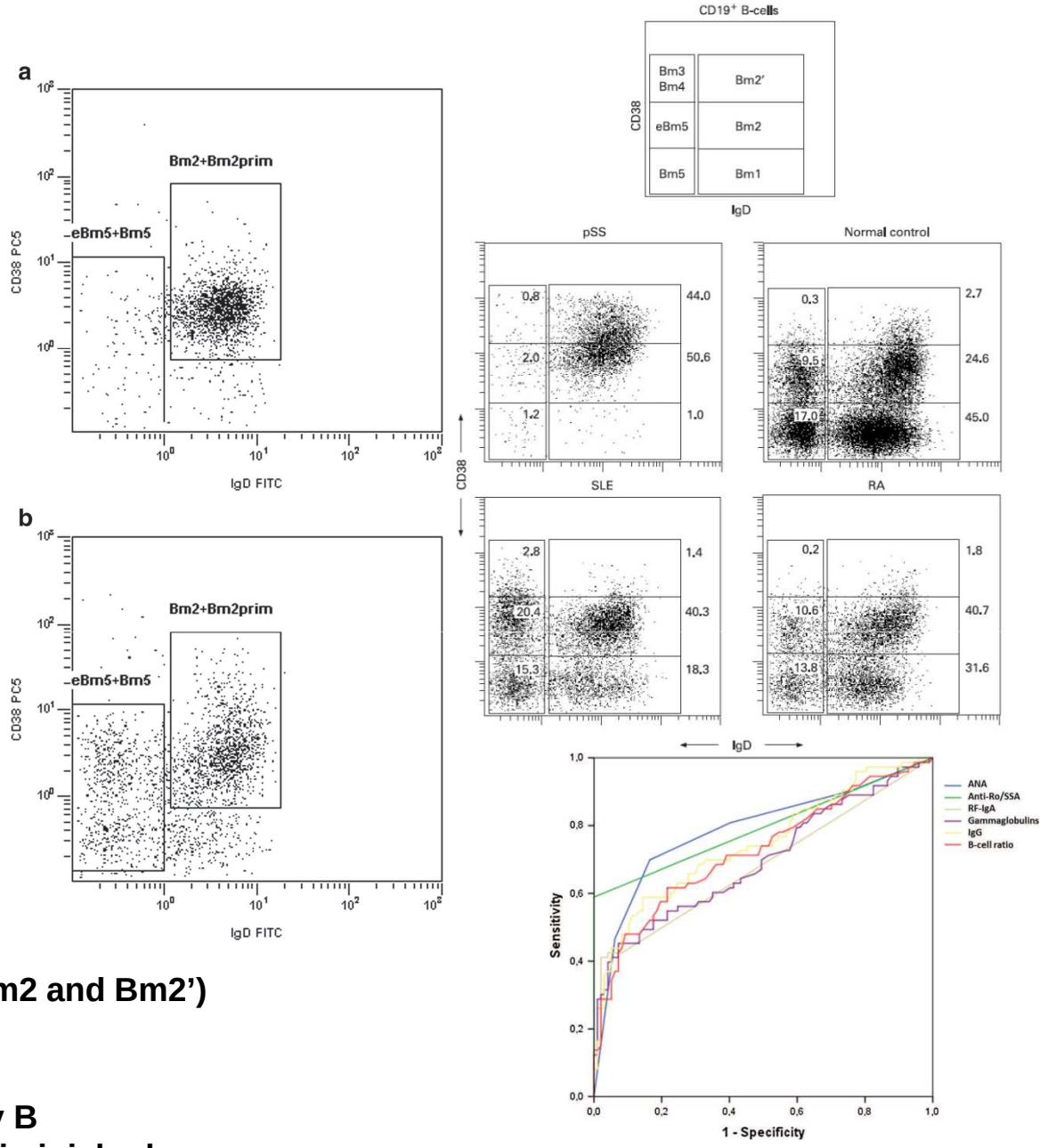
B-cell characteristics according to maturation stage and location

Subset	IgD	CD38	CD 23	CD27	CD20	CD19	Location
Pro-B	–	–	–	–	–	+	Marrow
Pre-B	–	–	–	–	+	+	
Bm1 (naive)	+	–	–	–	+	+	Peripheral sites
Bm2 (activated)	+	+	+	–	+	+	
Bm2′	+	++	+	–	+	+	
Bm3 (centroblast)	–	++	–	–	+	+	
Bm4 (centrocyte)	–	++	–	–	+	+	
Early Bm5	–	+	–	–	+	+	
Bm5	–	–	–	+	+	+	

Cornec J autoimmun 2012



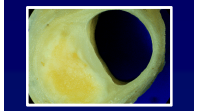




Germinal center founding cells (Bm2 and Bm2') are identified in the circulation.

The number of circulating memory B lymphocytes (eBm5 and Bm5) is diminished

Binard et al Ann Rheum Dis 2007
Cornec et al ART 2014



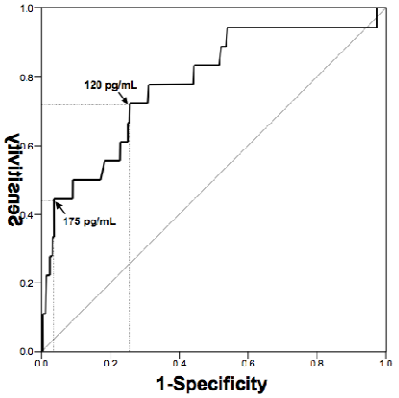
B Lymphocytes

Role of Fms-like Tyrosine Kinase 3 Ligand as a Potential Biologic Marker of Lymphoma in Primary Sjögren's Syndrome

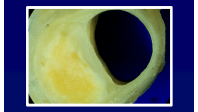
Gabriel J. Tobón,[1] Alain Saraux,[2] Jacques-Eric Gottenberg,[3] Luca Quartuccio,[4] Martina Fabris,[4] Raphaèle Seror,[5] Valérie Devauchelle-Pensec,[2] Jacques Morel,[6] Stéphanie Rist,[7] Xavier Mariette,[5] Salvatore De Vita,[4] Pierre Youinou,[8] and Jacques-Olivier Pers[2]

- Fms-like tyrosine kinase 3 Ligand (Flt3-Ligand)
- Cytokine having a role in ontogenesis of B cell
- Elevated in primary Sjogren' s syndrom
- Highly predictive of lymphoma with splenomegaly
- Regression logistique: 2 items splenomegaly (OR=56.4 [14.1-223.6]) and Flt3-L≥120 pg/mL (OR=17.3 [5.8-50.9]),

Figure 1



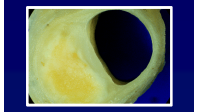
Tobon et al, Arthritis Rheum 2013



Autoimmune Epithelitis

- Epithelial cell apoptosis induced by lymphocytic infiltrates (Fas-FasL mechanisms)
- Expression by epithelial cells
  - Several TLRs (TLR2, TLR3, TLR4, and TLR7)
  - MHC-I, CD54/ICAM-I, CD40, CD95/Fas proteins, CD80, and CD86
  - HLA-II expression, encouraging ECs to shift toward antigen-presenting cells.
- Production by epithelial cell
  - chemokines (CXCL13, CCL19, and CCL21) which promote lymphocyte migration into the salivary glands.

This is also true on other epithelial cells justifying the term of « autoimmune epithelitis »

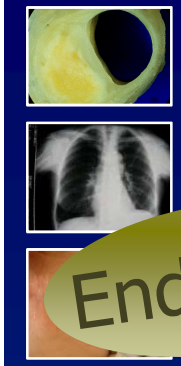


Exocrine signs

- Destruction of salivar and lachrymal acini lower than 70%

- Salivar and lachrymal secretion is controlled by cholinergic stimulation (acetylcholine) on muscarinic receptors M3 of the acini cells.
  – interleukine 1 and TNF-α, could inhibit it
  – anti muscarinic réceptors M3 have been detected in the sera
  – abnormal repartition of aquaporine 5, a canal of water, in salivary gland

Sjögren's syndrome physiopathology



Endocrine

Stress

EPITHELIUM

BAFF

Auto-Abs

La/SSB

La/SSB

MHC-II

FasL

CK receptor

ICAM.1

Fas

CD40

MHC-II

B7

BAFF

EXOSOMES

APOPTOSIS

Cytokines/ Chemokines IFN©

B

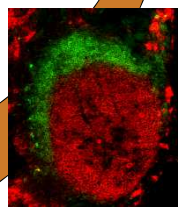
Ag-Release

Ag-Presentation

DC

DC

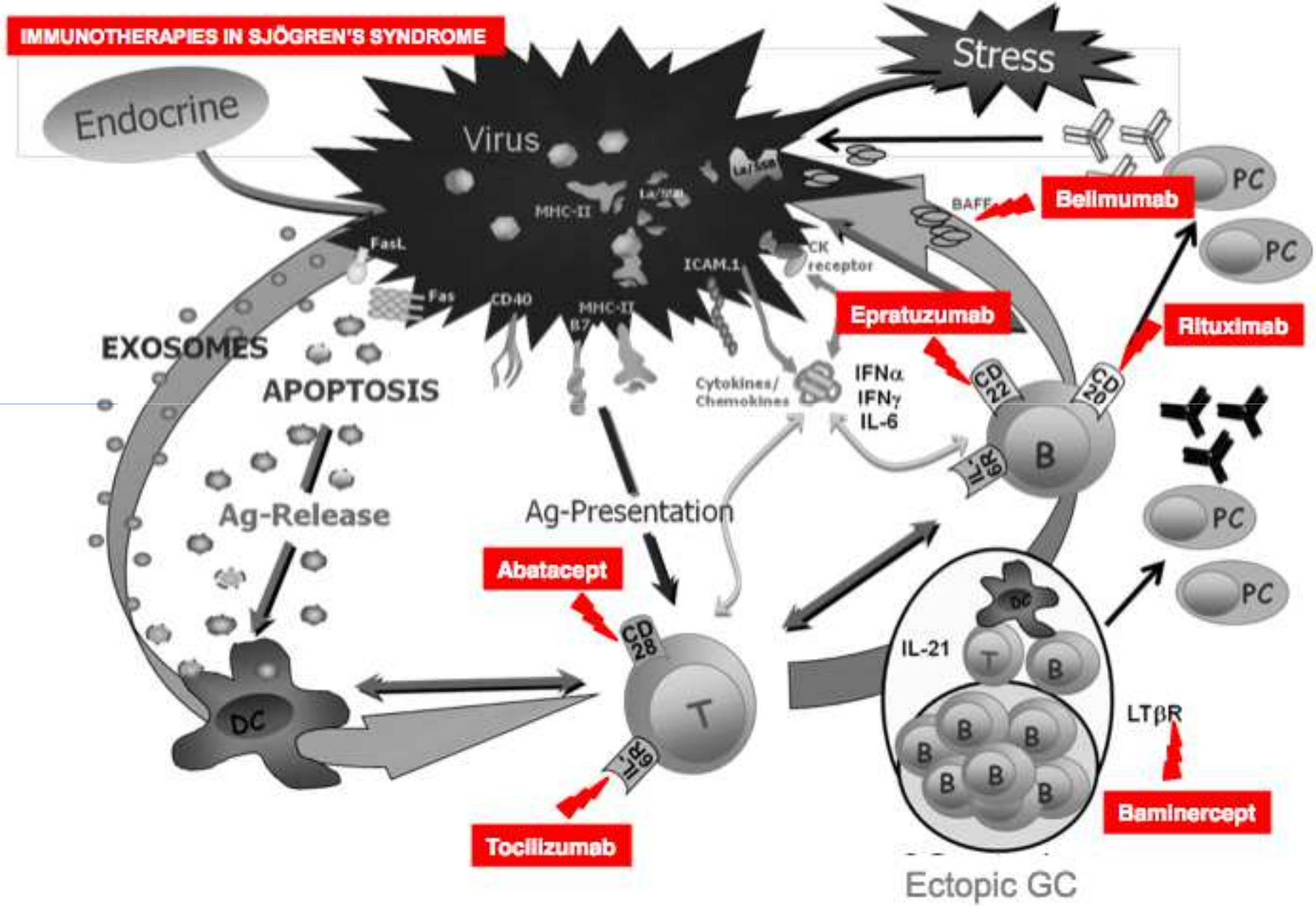
T



"Ectopic" GCs

Tzioufas, Moutsopoulos, 2012, Springer

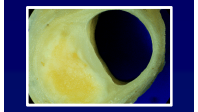
Do we have the good target ?



Possible approaches directed against potential targets in pSS, according to our knowledge of the immunopathology of the disease

Main immunopathological mechanisms involved in pSS	**Potential targets**
Epithelial cells acting as antigen-presenting cells	CD80-CD86
	ICAM
	CD40-CD28
	Cathepsin S
B-cell overactivity	B-cell specific molecules (CD20, CD22)
	BAFF
Interferon signature	IFN type I
	IFN γ, IL-7
Pro-inflammatory cytokines	IL-23, IL-17, IL-6
	IL-7, IL-18
Ectopic germinal centre formation	ICOS, LTβR
	IL-22, IL-21
Chemokines involved in lymphoid cell homing	CXCL13, CXCL 12
	CCL 19, CCL 21
Epigenetic modifications	Methylating enzymes (DNMT1)
	Demethylating enzymes (Gadd 45)

Saraux et al. Nature Reviews Rheumatology 2016 in press



Etanercept and Sjogren

double-blind, randomized pilot study of etanercept versus placebo therapy in 28 patients (n = 14 per group).

Inclusion criteria	outcome
criteria of Fox et al and American-European Consensus Group criteria for SS. Oral and ocular dryness evidence of active SS, as indicated by elevated ESR or IgG levels,	Efficacy was defined as meaningful improvement in 2 of the 3 SS disease domains: oral, ocular, and laboratory. Oral : ≥20% improvement in the patient's assessment of dry mouth by VAS or ≥20% improvement in total stimulated salivary flow. Ocular : ≥20% improvement in either the patient's assessment of dry eyes by VAS, the van Bijsterveld score, or the results of the Schirmer I test without anesthetic. Laboratory ≥20% improvement in the serum IgG level or the ESR.

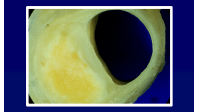
Sankar V. Arthritis Rheum. 2004. 2240-2245

Etanercept and Sjogren

12 weeks vs inclusion

	Etanercept (n = 14)	Placebo (n = 14)	
Dry mouth, by 100-mm VAS	−2 (−13, 2)	3 (−11, 10)	0.44
Dry eyes, by 100-mm VAS	1 (−6, 12)	−0.5 (−13, 5)	0.53
Schirmer I test, mm/5 minutes	−0.75 (−1.5, 1.00)	−0.50 (−2, 0)	0.55
Van Bijsterveld score	0 (−1.5, 0.5)	−0.25 (−1, 0)	0.96
Total stimulated saliva flow, ml/min	−0.033 (−0.31, 0.16)	−0.22 (−0.56, 0.13)	0.63
IgG, mg/dl	10 (−130, −50)	−30 (−140, 10)	0.82
ESR, mm/hour	−5.5 (−11, −4)	1.5 (−3, 6)	0.004

Sankar V. Arthritis Rheum. 2004. 2240-2245

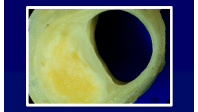


Infliximab and Sjogren

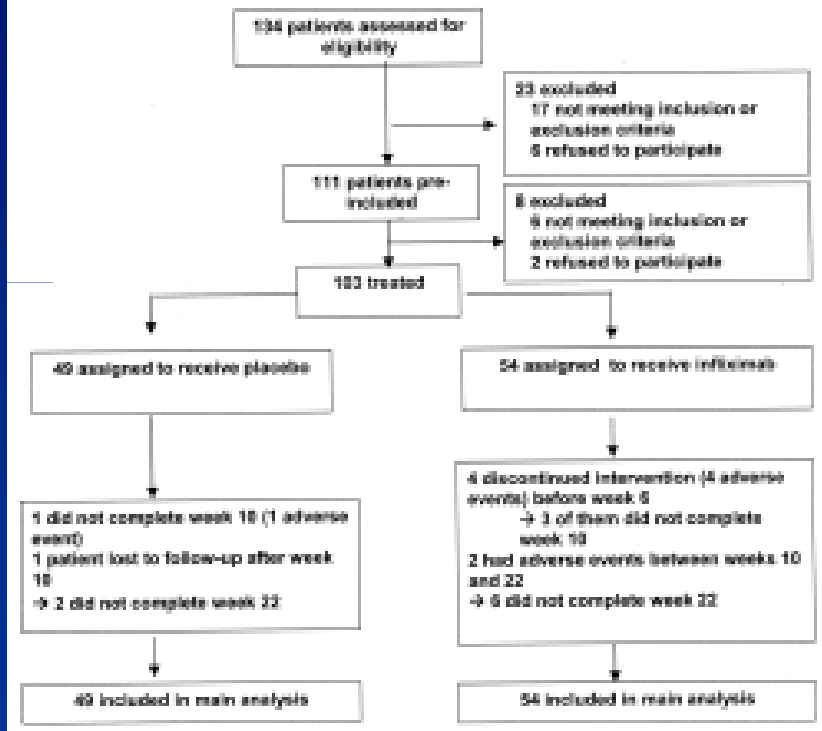
Infliximab 5mg/kg or pbo in 103 patients
Evaluation at 22 weeks

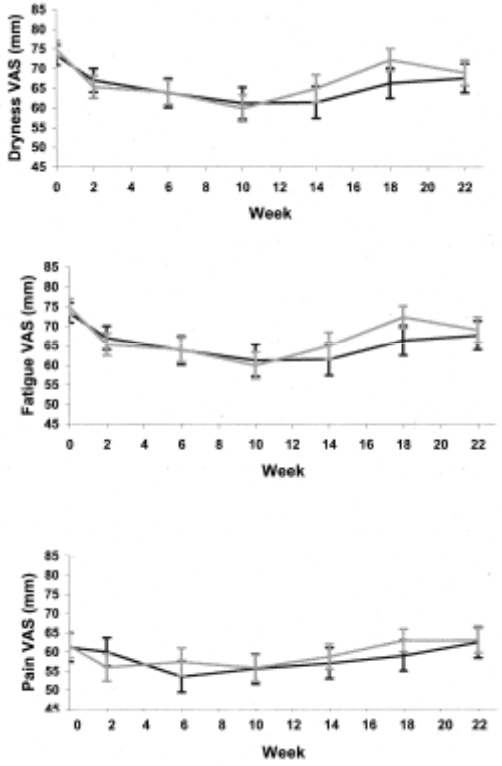
Inclusion criteria	outcome
New American-European Consensus Group criteria for SS (focus score ≥1 or tested positive for anti-Ro/SSA or anti-La/SSB) active disease: 3 visual analog scales (VAS) (0–100 mm) that evaluated joint pain, fatigue and the most disturbing dryness Patients had active disease if their values were >50 mm on 2 of the 3 VAS.	A favorable overall response was defined as the patient having a ≥30% improvement between weeks 0 and 10 in the values on 2 of the 3 VAS measuring joint pain, fatigue, and the most disturbing dryness.

Mariette X, Arthritis Rheum 2004; 50: 1270-1276



Infliximab and Sjogren





Mariette X, Arthritis Rheum 2004; 50: 1270-1276

Improvement of Sjögren's syndrome after two infusions of rituximab

8 (rituximab) and 9 (placebo) patients with pSS

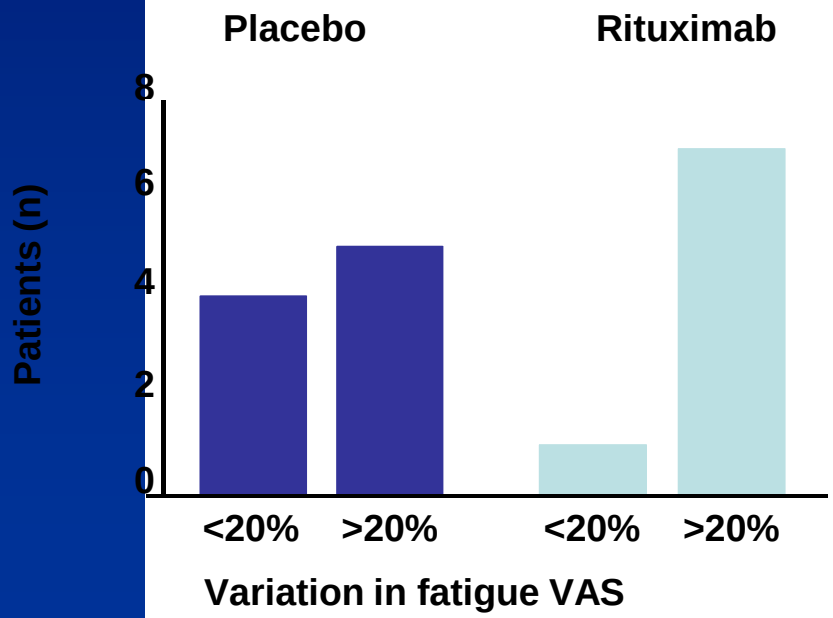
Inclusion criteria	outcome
American-European consensus criteria for primary SS Reduction of fatigue in Sjögren syndrome with rituximab: Results of a randomised, double-blind, placebo-controlled pilot study	20% reduction in fatigue VAS score at 6 months

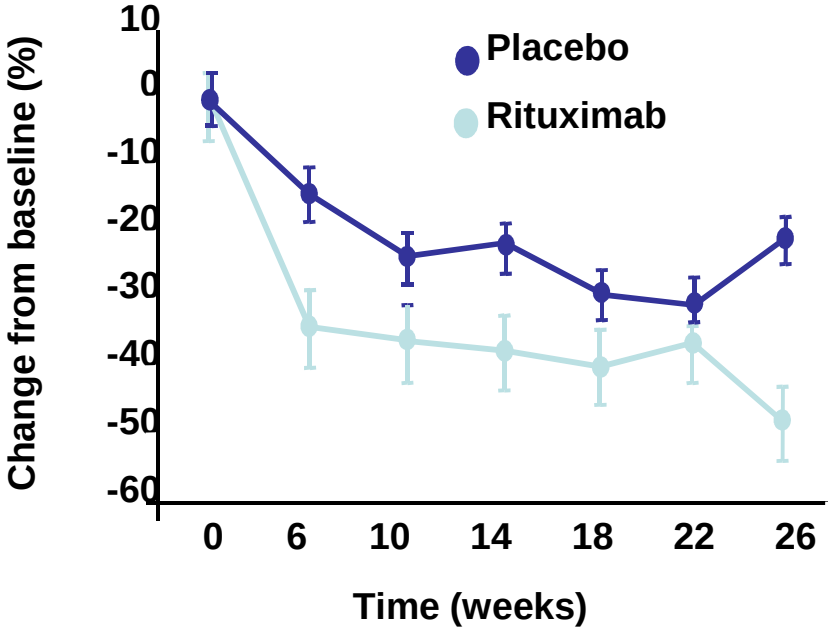
Dass S et al. Ann Rheum Dis 2008;67:1541–1544

Reduction of fatigue in Sjögren's syndrome with rituximab: Results of a randomised, double-blind, placebo-controlled pilot study

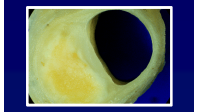
Results

- No significant difference between the 2 groups in primary endpoint
- Reduction in fatigue VAS vs inclusion rituximab group (p=0.001)





Dass S et al. Ann Rheum Dis 2008;67:1541–1544

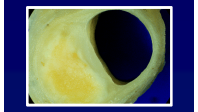


Rituximab treatment in pSS

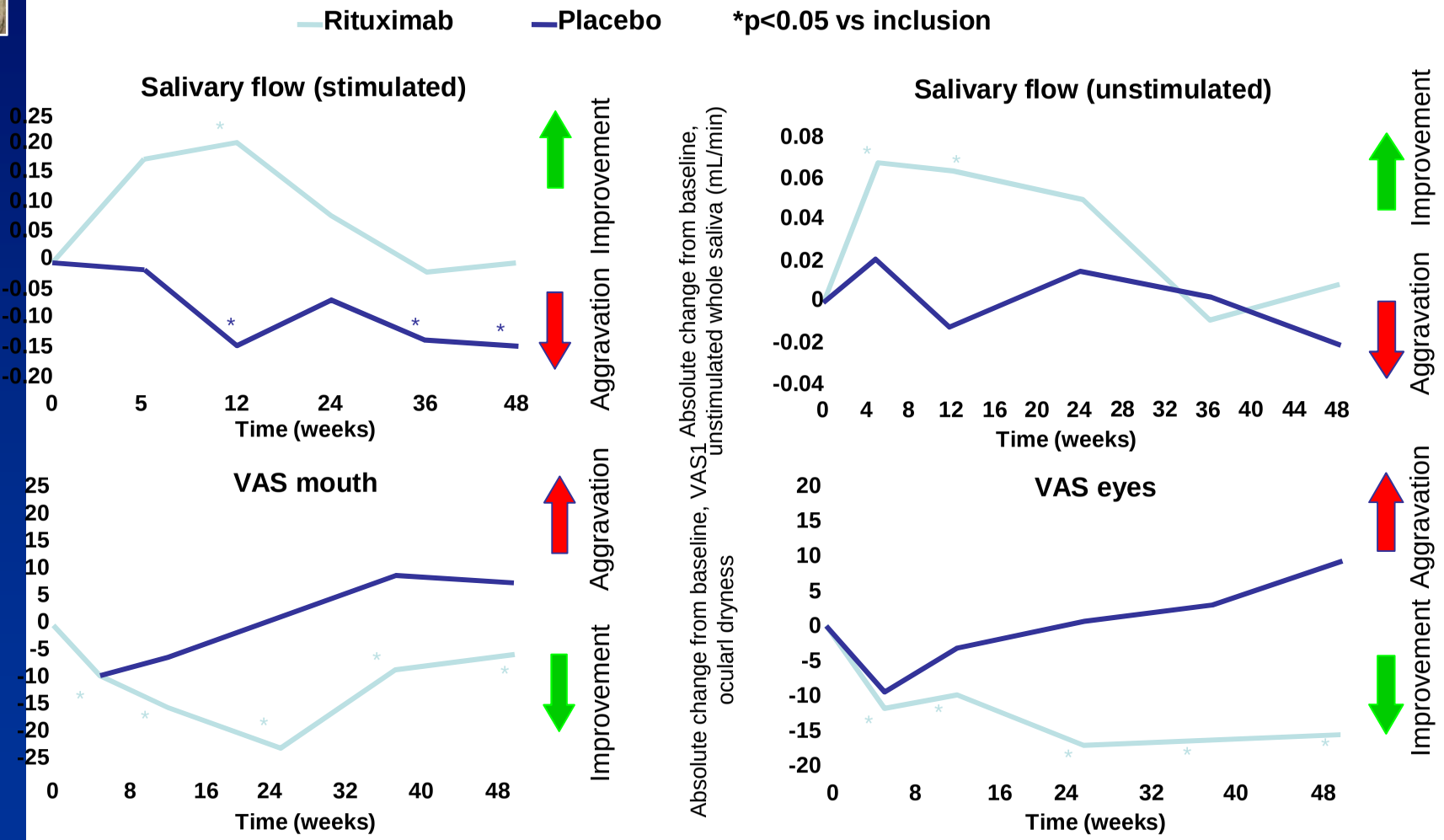
15 (rituximab) and 15 (placebo) patients with pSS

Inclusion criteria	outcome
American-European consensus criteria for primary SS Salivary flow (stimulated) >0.15 mL/min Anti-SSB or anti-SSA and RF SGLB grade III or IV	salivary flow (stimulated) at 12 weeks

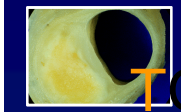
Meijer JM et al. Arthritis Rheum 2008;58(Suppl.):S430



Rituximab treatment in pSS



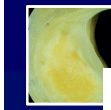
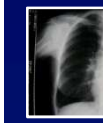
Meijer JM et al. Arthritis Rheum 2008;58(Suppl.):S430



TOLERANCE AND EFFICACY OF RITUXIMAB IN PRIMARY SJÖGREN SYNDROME

120 with pSS

Inclusion criteria	outcome
AECG criteria for pSS 2 of 4 VAS (0–100 mm) values >50 mm: on global scores of disease, pain, sicca and fatigue and recent (<10 years) and active disease as assessed by: autoantibodies (SSA or RF), or cryoglobulinaemia, or hypergammaglobulinaemia, or high level of beta 2-microglobulinaemia, or Hypocomplementaemia Or extra-glandular involvement pulmonary involvement, purpura or vasculitis, parotidomegaly, neurological involvement, arthritis, pancreatitis, tubulopathy, cytopenia, myositis, lymphadenopathy	30% improvement between Day 1 and Week 24 on 2 of the 4 VAS-measuring global scores of the disease (activity of the disease including extra-glandular manifestations), joint pain, fatigue and dryness


Annals of Internal Medicine | ORIGINAL RESEARCH

Treatment of Primary Sjögren Syndrome With Rituximab

A Randomized Trial

Valérie Devauchelle-Pensec, MD, PhD; Xavier Mariette, MD, PhD; Sandrine Jousse-Joulin, MD; Jean-Marie Berthelot, MD; Aleth Perdriger, MD, PhD; Xavier Puéchal, MD, PhD; Véronique Le Guern, MD, PhD; Jean Sibilia, MD, PhD; Jacques-Eric Gottenberg, MD, PhD; Laurent Chiche, MD, PhD; Eric Hachulla, MD, PhD; Pierre Yves Hatron, MD; Vincent Goeb, MD, PhD; Gilles Hayem, MD; Jacques Morel, MD, PhD; Charles Zarnitsky, MD; Jean Jacques Dubost, MD; Jacques Olivier Pers, MD, PhD; Emmanuel Nowak, PhD; and Alain Saraux, MD, PhD

Background: Primary Sjögren syndrome (pSS) is an autoimmune disorder characterized by ocular and oral dryness or systemic manifestations.

Objective: To evaluate efficacy and harms of rituximab in adults with recent-onset or systemic pSS.

Design: Randomized, placebo-controlled, parallel-group trial conducted between March 2008 and January 2011. Study personnel (except pharmacists), investigators, and patients were blinded to treatment group. (ClinicalTrials.gov: NCT00740948)

Setting: 14 university hospitals in France.

Patients: 120 patients with scores of 50 mm or greater on at least 2 of 4 visual analogue scales (VASs) (global disease, pain, fatigue, and dryness) and recent-onset (<10 years) biologically active or systemic pSS.

Intervention: Randomization (1:1 ratio) to rituximab (1 g at weeks 0 and 2) or placebo.

Measurements: Primary end point was improvement of at least 30 mm in 2 of 4 VASs by week 24.

Results: No significant difference between groups in the primary end point was found (difference, 1.0% [95% CI, −16.7% to 18.7%]). The proportion of patients with at least 30-mm decreases in at least two of the four VAS scores was higher in the rituximab group at week 6 (22.4% vs. 9.1%; $P = 0.036$). An improvement of at least 30 mm in VAS fatigue score was more common with rituximab at weeks 6 ($P < 0.001$) and 16 ($P = 0.012$), and improvement in fatigue from baseline to week 24 was greater with rituximab. Adverse events were similar between groups except for a higher rate of infusion reactions with rituximab.

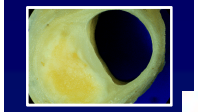
Limitation: Low disease activity at baseline and a primary outcome that may have been insensitive to detect clinically important changes.

Conclusion: Rituximab did not alleviate symptoms or disease activity in patients with pSS at week 24, although it alleviated some symptoms at earlier time points.

Primary Funding Source: Programme Hospitalier de Recherche Clinique 2010.

Ann Intern Med. 2014;160:233-242. www.annals.org

For author affiliations, see end of text.



Annals of Internal Medicine | ORIGINAL RESEARCH

Treatment of Primary Sjögren Syndrome With Rituximab

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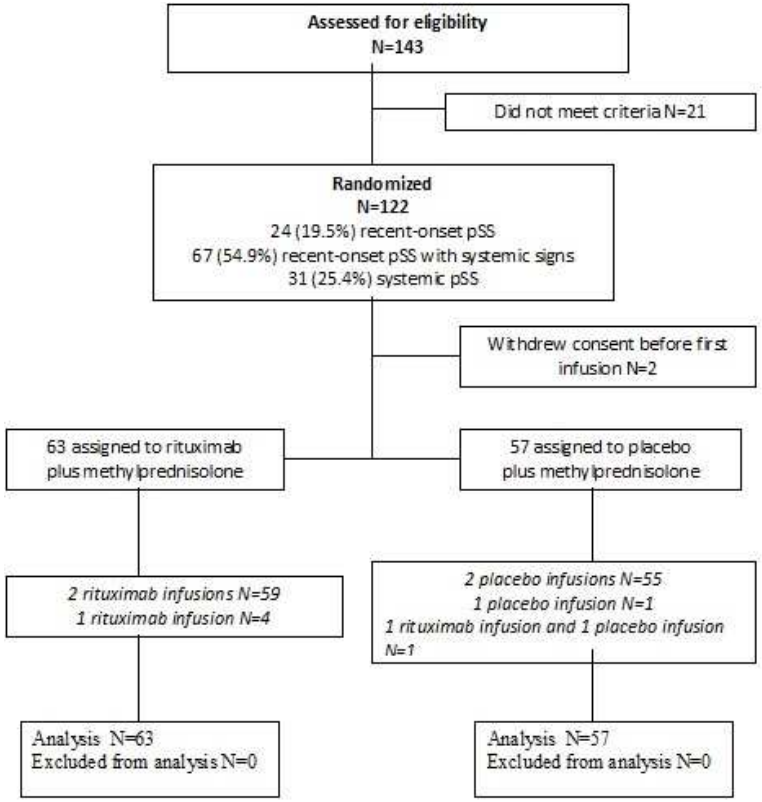
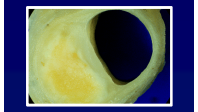
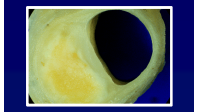
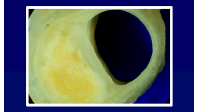




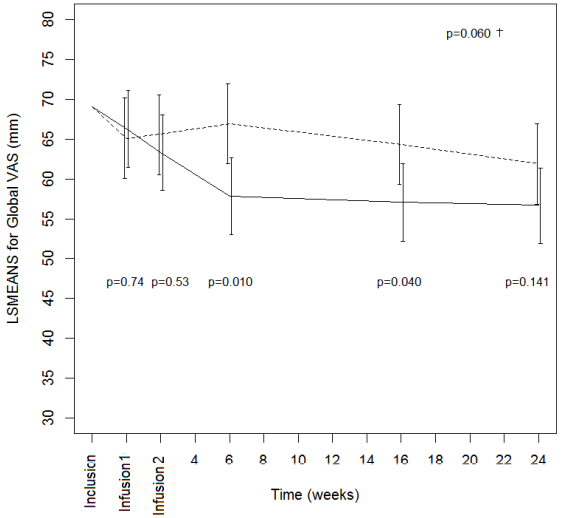
Variable	Week 6			
	Rituximab	Placebo	Difference (95% CI)	*P* Value
Patients with ≥ 30-mm improvement in VAS score, %†				
≥2 of 4 VASs‡	22.4	9.1	13.3 (0.8 to 25.8)	0.036
Global	15.8	8.0	7.8 (−8.6 to 24.1)	0.35
Pain	18.0	14.0	3.9 (−9.9 to 17.8)	0.57
Fatigue	34.7	8.2	26.6 (15.7 to 37.5)	<0.001
Dryness	16.6	8.6	8.0 (−3.7 to 19.7)	0.179
Mean improvement in ESSDAI score	0.8	1.0	−0.3 (−1.2 to 0.7)	0.60
Patients with physician-assessed improvements, %				
Disease activity	44.9	25.8	19.1 (4.4 to 33.7)	0.011
Systemic signs	7.8	18.0	−10.1 (−21.8 to 1.5)	0.089
Treatment efficacy	56.6	35.6	21.0 (9.3 to 32.7)	0.001
Mean improvements§				
Physician VAS, *mm*†	16.8	8.5	8.4 (4.2 to 12.5)	<0.001
Salivary flow rate, *mL/min*	0.01	0.02	−0.01 (−0.11 to 0.08)	0.80
Schirmer test result, *mm*	−0.4	−2.9	2.5 (0.0 to 5.0)	0.054
ESR, *mm/h*	2.4	2.8	−0.4 (−4.8 to 4.0)	0.84
Serum CRP level, *mg/L*	0.6	0.4	0.2 (−6.0 to 6.4)	0.95
IgG, *mg/L*	1.1	1.8	−0.7 (−2.3 to 0.9)	0.37
IgA, *mg/L*	0.3	−0.2	0.5 (0.1 to 1.0)	0.026
IgM, *mg/L*	0.2	0.0	0.2 (0.1 to 0.2)	0.004
C4 complement level, $g/L \times 10^{-4}$	0.0	−0.1	0.1 (−0.1 to 0.3)	0.32
β_2-Microglobulin level, $g/L \times 10^{-4}$	0.2	−0.2	0.4 (−0.4 to 1.1)	0.35
SF-36 score				
PCS	3.5	2.2	1.3 (−1.6 to 4.3)	0.36
MCS	5.1	2.8	2.2 (−2.5 to 6.9)	0.35

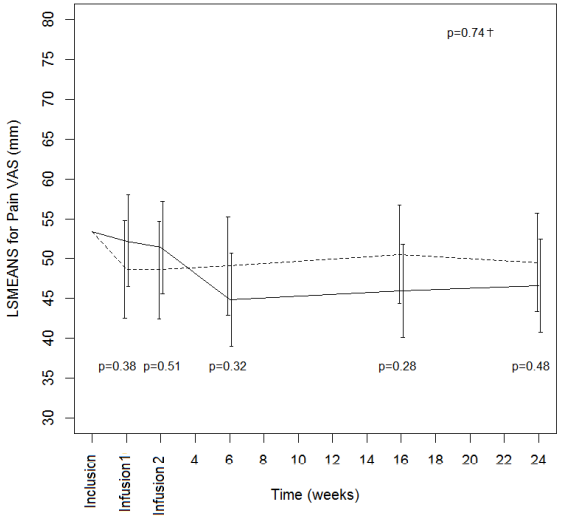


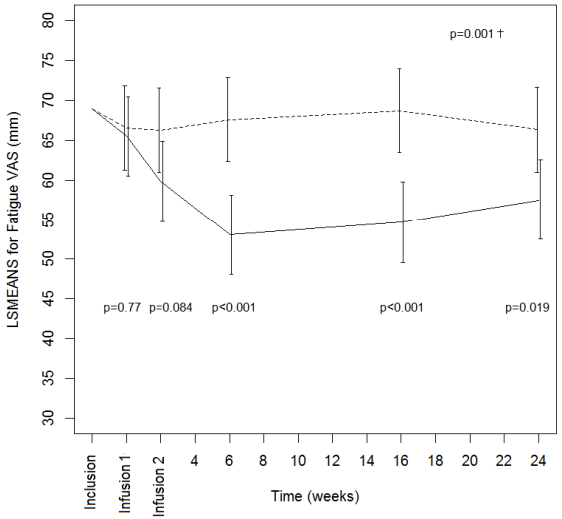
Week 16				Week 24			
Rituximab	Placebo	Difference (95% CI)	*P* Value	Rituximab	Placebo	Difference (95% CI)	*P* Value
26.3	17.0	9.3 (−1.5 to 20.0)	0.091	23.0	22.0	1.0 (−16.7 to 18.7)	0.91
20.5	18.2	2.4 (−11.2 to 16.0)	0.73	16.9	24.0	−7.1 (−19.1 to 4.9)	0.25
15.2	15.9	−0.7 (−8.6 to 7.2)	0.86	12.6	22.0	−9.4 (−26.7 to 8.0)	0.29
27.2	8.9	18.3 (4.1 to 32.6)	0.012	20.1	10.8	9.3 (−2.0 to 20.5)	0.105
21.1	13.6	7.5 (−5.4 to 20.4)	0.25	25.6	13.2	12.4 (−3.0 to 27.8)	0.114
1.6	2.0	−0.3 (−1.7 to 1.0)	0.66	1.2	1.7	−0.5 (−2.3 to 1.3)	0.57
41.6	30.6	10.9 (−3.7 to 25.6)	0.142	44.6	43.3	1.4 (−15.3 to 18.0)	0.87
16.8	14.2	2.6 (−9.1 to 14.4)	0.66	18.4	22.7	−4.3 (−16.4 to 7.9)	0.48
53.6	52.8	0.8 (−8.6 to 10.2)	0.87	48.8	56.4	−7.6 (−20.0 to 4.8)	0.23
16.2	12.6	3.6 (−1.9 to 9.2)	0.20	15.0	10.9	4.1 (−1.6 to 9.8)	0.157
−0.01	−0.03	0.02 (−0.07 to 0.11)	0.69	0.01	−0.04	0.04 (−0.04 to 0.13)	0.29
−0.6	−1.4	0.7 (−2.7 to 4.2)	0.67	0.0	−1.9	1.9 (−0.2 to 4.1)	0.080
3.6	−0.9	4.5 (−1.7 to 10.7)	0.155	6.4	2.7	3.7 (−1.8 to 9.1)	0.185
3.0	1.9	1.1 (−2.5 to 4.7)	0.55	1.9	2.2	−0.3 (−2.3 to 1.6)	0.74
1.6	0.7	0.9 (0.1 to 1.8)	0.021	1.7	0.5	1.2 (0.4 to 2.0)	0.003
0.4	−0.1	0.4 (0.0 to 0.9)	0.063	0.4	−0.2	0.5 (0.0 to 1.1)	0.047
0.3	0.0	0.2 (0.1 to 0.3)	<0.001	0.3	0.0	0.3 (0.2 to 0.4)	<0.001
0.2	−0.1	0.3 (0.0 to 0.5)	0.048	0.2	0.1	0.1 (−0.2 to 0.4)	0.55
1.0	−0.5	1.5 (0.6 to 2.4)	0.001	1.0	−0.6	1.6 (0.5 to 2.8)	0.004
3.2	2.2	1.1 (−1.8 to 3.9)	0.46	3.8	3.2	0.6 (−1.5 to 2.6)	0.58
3.2	0.8	2.3 (−0.6 to 5.2)	0.116	1.7	1.2	0.5 (−2.9 to 4.0)	0.76

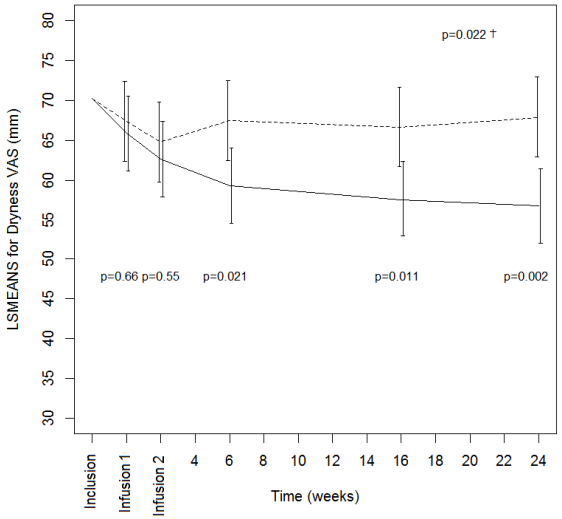


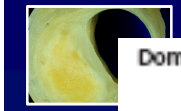
TEARS


p=0.060 †
LSMEANS for Global VAS (mm)
p=0.74 p=0.53 p=0.010 p=0.040 p=0.141
Inclusion Infusion 1 Infusion 2
Time (weeks)


p=0.74 †
LSMEANS for Pain VAS (mm)
p=0.38 p=0.51 p=0.32 p=0.28 p=0.48
Inclusion Infusion 1 Infusion 2
Time (weeks)


p=0.001 †
LSMEANS for Fatigue VAS (mm)
p=0.77 p=0.084 p<0.001 p<0.001 p=0.019
Inclusion Infusion 1 Infusion 2
Time (weeks)


p=0.022 †
LSMEANS for Dryness VAS (mm)
p=0.66 p=0.55 p=0.021 p=0.011 p=0.002
Inclusion Infusion 1 Infusion 2
Time (weeks)



Domain	Baseline		Week 6		Week 16		Week 24	
	Rituximab (*n* = 63)	Placebo (*n* = 57)	Rituximab (*n* = 61)	Placebo (*n* = 56)	Rituximab (*n* = 60)	Placebo (*n* = 55)	Rituximab (*n* = 61)	Placebo (*n* = 54)
Constitutional	None: 47 Low: 5 Moderate: 11	None: 41 Low: 4 Moderate: 12	None: 51 Low: 0 Moderate: 10	None: 45 Low: 0 Moderate: 11	None: 48 Low: 1 Moderate: 11	None: 41 Low: 0 Moderate: 14	None: 48 Low: 2 Moderate: 11	None: 41 Low: 0 Moderate: 13
Lymphadenopathy	None: 59 Low: 3 Moderate: 1	None 54 Low: 3 Moderate: 0	None: 57 Low: 4 Moderate: 0	None: 54 Low: 2 Moderate: 0	None: 58 Low: 2 Moderate: 0	None: 54 Low: 0 Moderate: 1	None: 58 Low: 2 Moderate: 1	None: 52 Low: 2 Moderate: 0
Glandular	None: 45 Low: 10 Moderate: 8	None: 42 Low: 6 Moderate: 9	None: 44 Low: 13 Moderate: 4	None: 40 Low: 12 Moderate: 4	None: 47 Low: 11 Moderate: 2	None: 42 Low: 9 Moderate: 4	None: 47 Low: 9 Moderate: 5	None: 40 Low: 8 Moderate: 6
Articular	None: 33 Low: 12 Moderate: 13 High: 5	None: 30 Low: 14 Moderate: 9 High: 4	None: 33 Low: 12 Moderate: 13 High: 3	None: 31 Low: 16 Moderate: 7 High: 2	None: 33 Low: 17 Moderate: 8 High: 2	None: 31 Low: 16 Moderate: 6 High: 2	None: 36 Low: 16 Moderate: 5 High: 4	None: 32 Low: 14 Moderate: 4 High: 4
Cutaneous	None: 58 Low: 1 Moderate: 2 High: 2	None: 55 Low: 0 Moderate: 1 High: 1	None: 59 Low: 0 Moderate: 1 High: 1	None: 54 Low: 0 Moderate: 1 High: 1	None: 59 Low: 0 Moderate: 1 High: 0	None: 53 Low: 0 Moderate: 0 High: 2	None: 59 Low: 0 Moderate: 2 High: 0	None: 53 Low: 0 Moderate: 0 High: 1
Pulmonary	None: 52 Low: 10 Moderate: 1	None: 40 Low: 11 Moderate: 6	None: 49 Low: 11 Moderate: 1	None: 40 Low: 12 Moderate: 4	None: 49 Low: 11 Moderate: 0	None: 44 Low: 9 Moderate: 2	None: 49 Low: 11 Moderate: 1	None: 43 Low: 8 Moderate: 3
Renal	None: 57 Low: 1 Moderate: 0 High: 5	None: 56 Low: 0 Moderate: 0 High: 1	None: 55 Low: 1 Moderate: 0 High: 5	None: 55 Low: 0 Moderate: 0 High: 1	None: 55 Low: 1 Moderate: 0 High: 4	None: 55 Low: 0 Moderate: 0 High: 0	None: 55 Low: 1 Moderate: 0 High: 5	None: 53 Low: 0 Moderate: 0 High: 1
Muscular	None: 61 Low: 1 Moderate: 1	None: 56 Low: 1 Moderate: 0	None: 59 Low: 1 Moderate: 1	None: 55 Low: 1 Moderate: 0	None: 58 Low: 1 Moderate: 1	None: 54 Low: 1 Moderate: 0	None: 59 Low: 1 Moderate: 1	None: 53 Low: 1 Moderate: 0
PNS	None: 54 Low: 4 Moderate: 4 High: 1	None: 47 Low: 2 Moderate: 8 High: 0	None: 52 Low: 3 Moderate: 6 High: 0	None: 46 Low: 2 Moderate: 8 High: 0	None: 51 Low: 4 Moderate: 5 High: 0	None: 46 Low: 2 Moderate: 7 High: 0	None: 51 Low: 7 Moderate: 3 High: 0	None: 46 Low: 3 Moderate: 5 High: 0
CNS	None: 63 Low: 0 Moderate: 0	None: 57 Low: 0 Moderate: 0	None: 61 Low: 0 Moderate: 0	None: 56 Low: 0 Moderate: 0	None: 60 Low: 0 Moderate: 0	None: 55 Low: 0 Moderate: 0	None: 61 Low: 0 Moderate: 0	None: 54 Low: 0 Moderate: 0
Hematologic	None: 39 Low: 22 Moderate: 2	None: 34 Low: 18 Moderate: 5	None: 34 Low: 22 Moderate: 5	None: 35 Low: 18 Moderate: 3	None: 33 Low: 22 Moderate: 5	None: 35 Low: 16 Moderate: 4	None: 36 Low: 22 Moderate: 3	None: 34 Low: 17 Moderate: 3
Biological	None: 27 Low: 19 Moderate: 17	None: 24 Low: 15 Moderate: 18	None: 32 Low: 12 Moderate: 17	None: 25 Low: 13 Moderate: 18	None: 30 Low: 9 Moderate: 21	None: 22 Low: 16 Moderate: 17	None: 29 Low: 12 Moderate: 20	None: 20 Low: 17 Moderate: 17

CNS = central nervous system; ESSDAI = European League Against Rheumatism Sjögren Syndrome Disease Activity Index; PNS = peripheral nervous system.

FATIGUE (PBO)
0
20
40
60
80
100
Inclusion
Infusion 1
Infusion 2
6
10
14
18
22
Time (weeks)

FATIGUE (RTX)
0
20
40
60
80
100
Inclusion
Infusion 1
Infusion 2
6
10
14
18
22
Time (weeks)

FATIGUE (PBO)
0
20
40
60
80
100
Inclusion
Infusion 1
Infusion 2
6
10
14
18
22
Time (weeks)

FATIGUE (RTX)
0
20
40
60
80
100
Inclusion
Infusion 1
Infusion 2
6
10
14
18
22
Time (weeks)

DRYNESS (PBO)
0
20
40
60
80
100
Inclusion
Infusion 1
Infusion 2
6
10
14
18
22
Time (weeks)

DRYNESS (RTX)
0
20
40
60
80
100
Inclusion
Infusion 1
Infusion 2
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Time (weeks)

DRYNESS (PBO)
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Infusion 1
Infusion 2
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Time (weeks)

DRYNESS (RTX)
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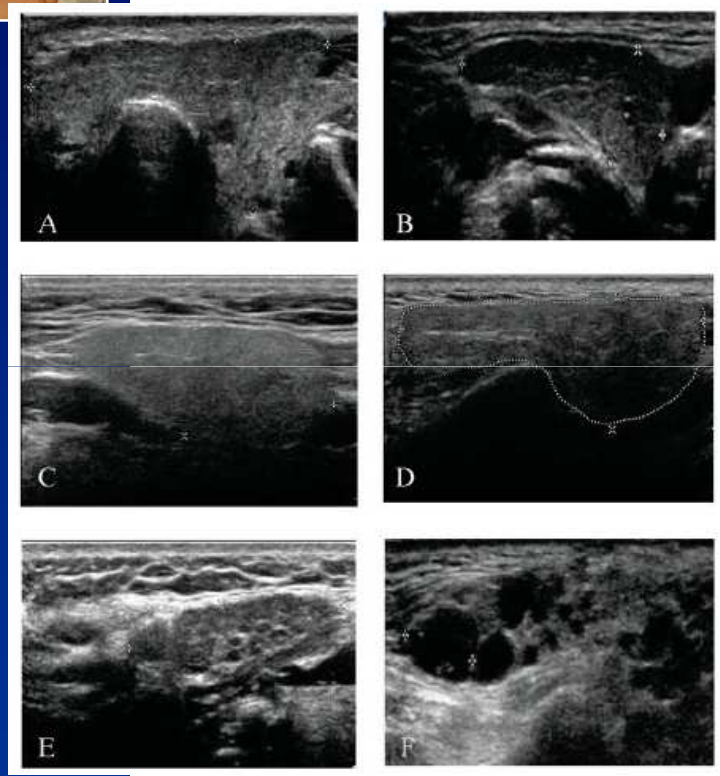
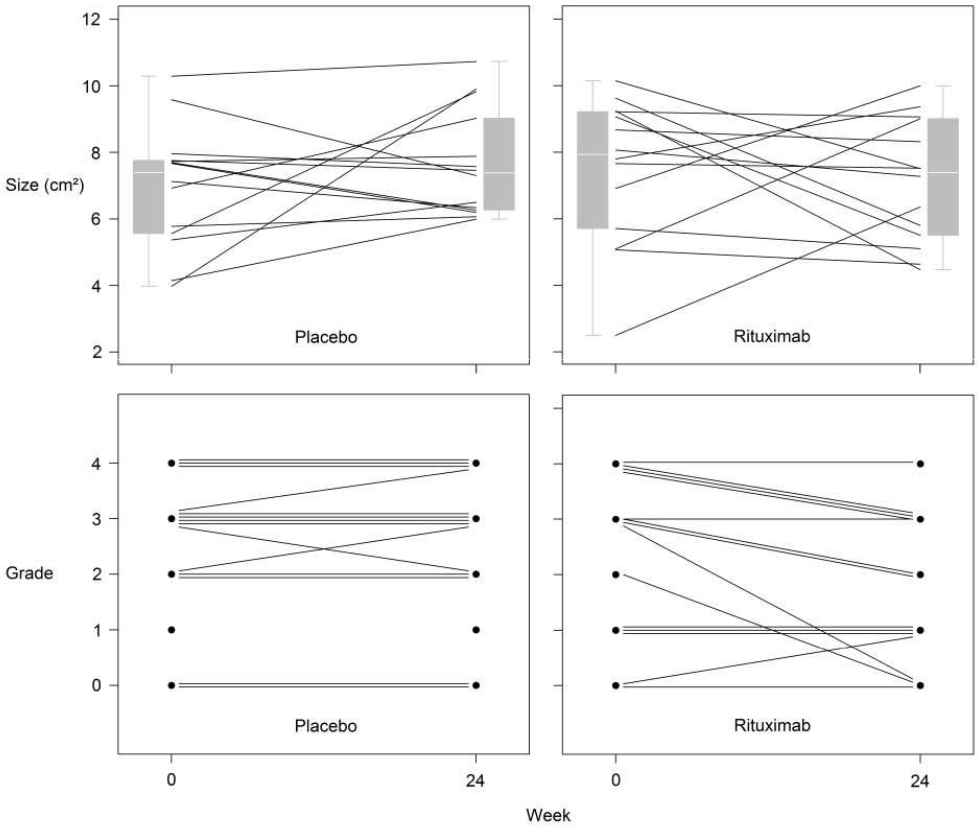
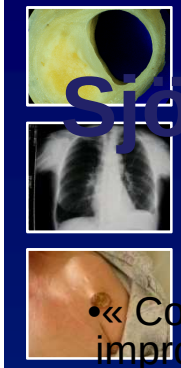
80
100
Inclusion
Infusion 1
Infusion 2
6
10
14
18
22
Time (weeks)

Ultrasonographic Salivary Gland Response to Rituximab in Primary Sjögren's Syndrome





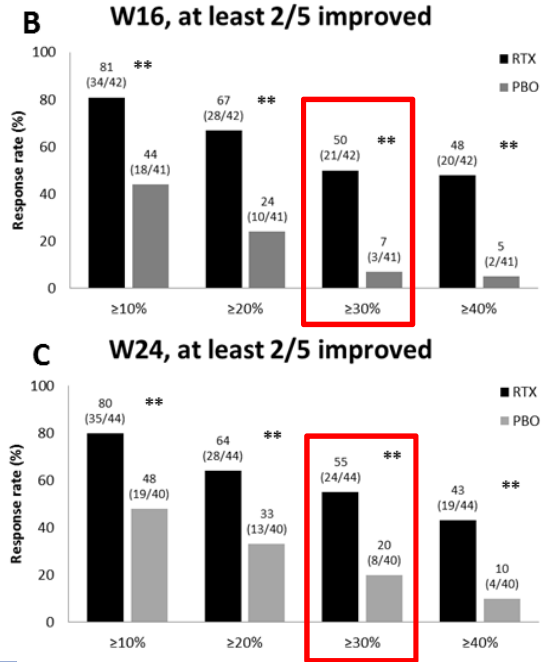
S Jousse-Joulin, Arthritis Rheumatol, 2015

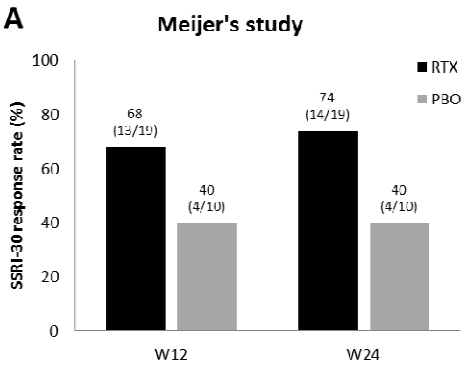


Sjögren's Syndrome Responder Index (SSRI)

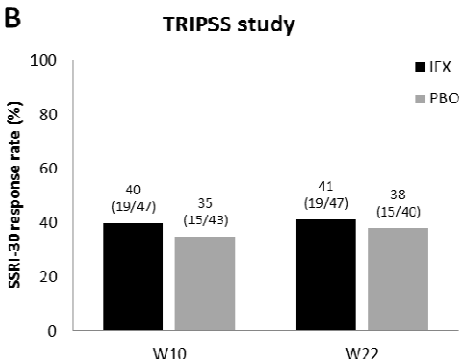
- « Core set » of outcome measures improved by rituximab:
  - Oral dryness VAS
  - Ocular dryness VAS
  - Fatigue VAS
  - UWSF
  - ESR

- SSRI-30: ≥30% improvement of at least 2/5 outcome measures





Meijer et al (2010)
rituximab (n=20) vs placebo (n=10)



TRIPPS (2004)
infliximab (n=55) vs placebo (n=55)

Responders: QOL improvement (SF36)
Systemic activity improvement

Rheumatology 2015

PLOS ONE | DOI:10.1371/journal.pone.0133907 September 14, 2015

Which and How Many Patients Should Be Included in Randomised Controlled Trials to Demonstrate the Efficacy of Biologics in Primary Sjögren's Syndrome?

Valérie Devauchelle-Pensec[1,2], Jacques-Eric Gottenberg[3], Sandrine Jousse-Joulin[1,2], Jean-Marie Berthelot[4], Aleth Perdriger[5], Eric Hachulla[6], Pierre Yves Hatron[6], Xavier Puechal[7], Véronique Le Guern[7], Jean Sibilia[3], Laurent Chiche[8], Vincent Goeb[9], Olivier Vittecoq[10], Claire Larroche[11], Anne Laure Fauchais[12], Gilles Hayem[13], Jacques Morel[14], Charles Zarnitsky[15], Jean Jacques Dubost[16], Philippe Dieudé[17], Jacques Olivier Pers[2], Divi Cornec[1,2], Raphaele Seror[18], Xavier Mariette[18], Emmanuel Nowak[19], Alain Saraux[1,2]*

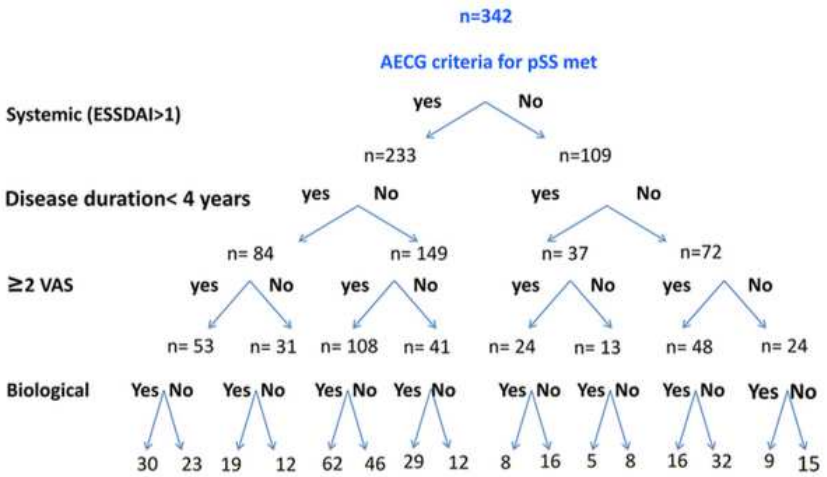
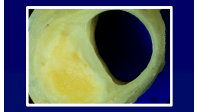


Fig 2. Number of patients in the ASSESS cohort fulfilling each inclusion criteria set. First step: AECG criteria. Second step: systemic disease (ESSDAIhigher to 2). Third step: disease duration less than 4 years. Fourth step: More than two VAS/3 higher to 50/100 mm. Fifth step: biological activity (pSS, primary Sjögren's syndrome; AECG, American-European Consensus Group; ESSDAI, EULAR Sjögren Syndrome Disease Activity Index; VAS, visual analog scale (100-mm line); BA, biological activity).

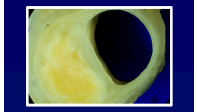
Table 3. Number of patients to include in future randomised controlled trials of rituximab in primary Sjögren's syndrome according to the primary endpoint assessed at weeks 6, 16, and 24.

Patient improvement	**At week 6, P vs. R; N: sample size**			**At Week 16, P vs. R; N: sample size**			**At week 24, P vs. R; N: sample size**		
VAS scores	higher or equal **10 mm**	**higher or equal 20 mm**	**higher or equal 30 mm**	**higher or equal 10 mm**	**higher or equal 20 mm**	**higher or equal 30 mm**	**higher or equal 10 mm**	**higher or equal 20 mm**	**higher or equal 30 mm**
Disease	33.8 vs. 43.8 N = 782	18.0 vs. 31.7 N = 338	8.0 vs. 15.8 N = 588	34.0 vs 53.3 N = 226	21.2 vs 33.4 N = 448	18.2 vs 20.5 N = 9432	35.8 vs 52.7 N = 292	26.3 vs 36.0 N = 754	24.0 vs 16.9 N = NA
Pain	34.1 vs. 34.4 N higher to 10000	25.5 vs. 28.7 N = 6180	14.0 vs. 18.0 N = 2734	30.1 vs 34.6 N = 3478	15.8 vs 21.8 N = 1394	15.9 vs 15.2 N = NA	39.2 vs 44.1 N = 3256	33.0 vs 25.7 N = NA	22.0 vs 12.6N = NA
Fatigue	30.8 vs. 54.7 N = 148	17.1 vs. 39.4 N = 142	8.2 vs. 34.7 N = 88	21.9 vs 47.0 N = 126	15.0 vs 38.7 N = 124	8.9 vs 27.2 N = 158	31.2 vs 51.5 N = 202	17.8 vs 29.2 N = 466	10.8 vs 20.1 N = 514
Dryness	25.3 vs. 45.7 N = 190	13.0 vs. 29.9 N = 206	8.6 vs. 16.6 N = 586	32.1 vs 53.9 N = 178	16.5 vs 26.2 N = 598	13.6 vs 21.1 N = 850	26.3 vs 51.3 N = 132	17.2 vs 31.0 N = 328	13.2 vs 25.6 N = 348
ESSPRI	33.3 vs. 49.2 N = 324	21.6 vs. 32.5 N = 556	7.3 vs. 22.5 N = 196	24.2 vs 41.0 N = 266	16.7 vs 27.5 N = 498	10.2 vs 13.5 N = 3130	29.1 vs 44.3 N = 340	22.2 vs 28.9 N = 1388	13.0 vs 13.1 N higher to 10000
Patient improvement	**At Week 6, P vs. R; N: sample size**			**At Week 16, P vs. R; N: sample size**			**At week 24, P vs. R; N: sample size**		
Number of VAS scores improved by 30 mm (at least)	**higher or equal 1**	**higher or equal 2**	**higher or equal 3**	**higher or equal 1**	**higher or equal 2**	**higher or equal 3**	**higher or equal 1**	**higher or equal 2**	**higher or equal 3**
	26.7 vs. 49.5N = 158	9.1 vs. 22.4 N = 262	3.1 vs. 11.1 N = 370	24.5 vs 50.0N = 126	17.0 vs 26.3 N = 656	10.1 vs 6.5 N = NA	37.8 vs 42.2 N = 3980	22.0 vs 23.0 N higher to 10000	11.9 vs 9.6 N = NA
Improvement in SGUS grade	**higher or equal 1 grade**			**higher or equal 1 grade**			**higher or equal 1 grade**		
	ND			ND			1/14 (7.1 percent) vs. 7/14 (50.0 percent) N = 42		



Controlled therapeutic trials of biologics in primary Sjögren's syndrome

Author	Inclusion criteria	Treatment	N	Primary endpoint	Significance
[49]	AECG, dryness and active pSS (ESR or IgG levels)	Etanercept	14	2 of 3 domains among dry mouth, dry eyes, and IgG level or ESR	No
TRIPPS[48]	AECG and VAS (pain, fatigue, and the most disturbing dryness)	Infliximab	103	2 of 3 VASs for joint pain, fatigue, and the most disturbing dryness	No
[42]	AECG and VAS fatigue	Rituximab	17	VAS fatigue	No on primary objective but improvement
[40]	AECG and stimulated whole saliva and autoantibodies and SGB grade III or IV	Rituximab	30	Stimulated whole saliva flow rate	Yes
TEARS [50]	AECG and recent disease with biological activity or systemic manifestations and VAS (global disease, pain, fatigue, and dryness)	Rituximab	122	2 or 4 VASs	No, but slight efficacy on fatigue and sicca
[135]	AECG and fatigue	Anakinra	26	VAS fatigue	No
TRACTISS [52, 136]	AECG, fatigue, oral dryness, anti-Ro antibodies, and unstimulated salivary flow rate >0 mL/min with systemic involvement if disease duration >10 years	Rituximab	110	VAS fatigue or oral dryness score	No, but slight efficacy on sicca



Controlled therapeutic trials of biologics in primary Sjögren's syndrome

Author	Inclusion criteria	Treatment	N	Primary endpoint
Gottenberg JE, France	AECG *and* anti-SSA or anti-SSB *and* ESSDAI ≥5	Tocilizumab (humanized monoclonal antibody against the interleukin-6 receptor)	110	ESSDAI
Bootsma H, The Netherlands	AECG and ESSDAI ≥5	Abatacept (fusion protein composed of the Fc region of the IgG1 fused to the extracellular domain of CTLA-4)	88	ESSDAI
Novartis	AECG and ESSDAI score ≥6	CFZ533 (Monoclonal antibody that binds CD40 and prevents its binding with CD154)	42	ESSDAI
Novartis	AECG and ESSDAI value ≥6; Elevated serum ANA titres at screening (≥1:160); anti-SSA and/or anti-SSB antibodies; Stimulated whole salivary flow rate at screening >0 mL/min	VAY736 **(**fully human monoclonal antibody targeting BAFF-R)	27	ESSDAI
UCB Pharma	AECG and anti-SSA/Ro (Ro-52 and Ro-60) and/or anti SSB/La	UCB5857 (small molecule, inhibitor of PI3K delta)	58	ESSDAI
MedImmune	AECG and ESSDAI score ≥6	AMG 557/MEDI5872 (Human monoclonal antibody targeting B7 related protein)	42	ESSDAI
GlaxoSmithKline	AECG and ESSDAI score ≥5 Anti-SSA and/or anti-SSB antibodies; Stimulated whole salivary flow rate at screening >0 mL/min or evidence of glandular reserve function (stimulated baseline salivary flow >0.05 mL/min); Symptomatic oral dryness (≥5/10 on patient- completed numeric rating scale).	Belimumab (human monoclonal antibody that inhibits BAFF) and Rituximab (anti CD20) co-administration	70	Number of participants with AE and SAEs

Controlled therapeutic trials of biologics in primary Sjögren's syndrome

Author	Inclusion criteria	Treatment	N	Primary endpoint
National Institute of Allergy and Infectious Diseases	AECG and Stimulated salivary flow ≥0.1 mL/minute (min) (at screening), one or more systemic manifestations	Baminercept (Lymphotoxin-beta Receptor Fusion Protein)	72	Stimulated whole salivary flow
Jing He, Peking University, China	AECG and ESSDAI score ≥6	Low-dose IL-2	60	ESSDAI
Gabor Illei, National Institutes of Health Clinical Center, US	AECG and one or more of the following: ESR >25 mm/h for men; ESR>42 mm/h for women; Serum IgG level ≥1750 mg/dL; Serum CRP level ≥0.8 mg/dL Stimulated salivary flow ≥0.1 mL/min Minor salivary gland biopsy with a focus score ≥4 Ocular staining score ≥3 in at least one eye at study inclusion	Raptiva (Humanised Anti-CD-11a)	10	Improvement in 2/3 of salivary flow, salivary gland biopsy, and tear flow
Zhanguo Li, Beijing University, China	2002 or 2012 pSS criteria; interstitial pneumonitis	Cyclosporine A +glucocorticoid	240	Forced vital capacity

Conclusion

- New definition
- New tools
- Treatment but only symptomatic
- Immunopathology
- No biologics with label
- But many ongoing studies

Aknowledgement

- Divi Cornec, Sandrine Jousse-Joulin, Thierry Marhadour, Dewi Guellec, Valerie Devauchelle-pensec, Rheumatology,
- Jacques olivier Pers and Sylvie Boisramé-Gastrin, Dentist center
- Béatrice Cochener, Ophtalmology,
- Anne-Marie Roguedas-Contios, Dermatology,
- Myriam Chastaing, Véronique Griner-Abraham, psychiatry,
- Francis Couturaud, Pneumology,
- Jean Baptiste Noury and Steeve Genestet, Neurology,
- Catherine Hanrotel, Nephrology,
- Pascale Marcorelles, Anatomopathology,
- Sebastian Costa, anatomopathology,
- Yves Gauvin, Otorinolaryngology,

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