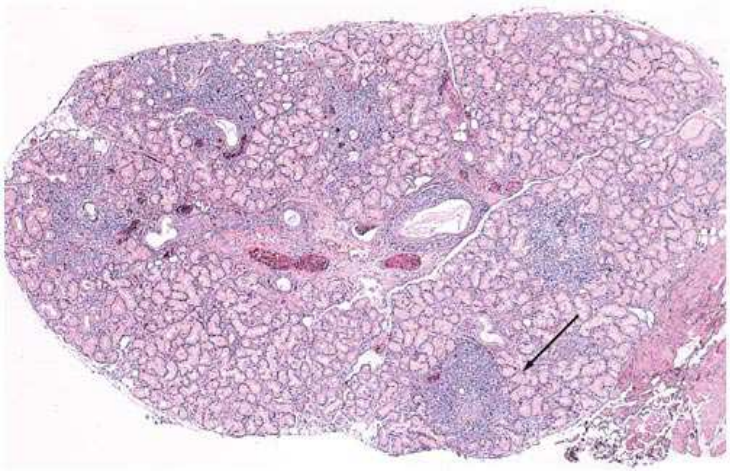
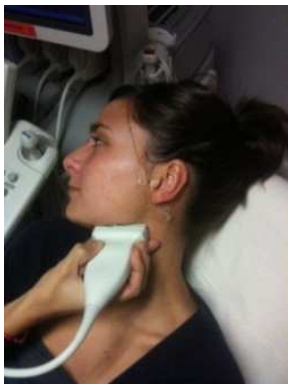
Diagnostic et Prise en charge du syndrome de Sjogren en 2015





Pr A Saraux
Chu de la Cavale Blanche
Brest

Prévalence de la maladie

Table 2 A summary of studies on the prevalence of primary Sjögren's syndrome according to diagnostic criteria used

Author, year	Country	Population size (N)	Criteria	Prevalence % (95% CI)
Zhang et al,1995[19]	People's Republic of China	2,066	Copenhagen	0.77
			San Diego	0.34 (0.44–1.25)
Birlik et al, 2009[12]	Turkey	2,835	European	0.35 (0.10–0.45)
			AECG	0.21 (0.03–0.29)
Kabasakal et al, 2006[13]	Turkey	831	European	0.56 (0.92–2.66)
			AECG	0.72 (0.33–1.57)
Miyasaka,1995[20]	Japan			0.03
Bowman et al, 2004[17]	UK	548	AECG	0.4 (0.04–1.32)
Thomas et al,1998[18]	UK	616	European	2.1 (1.13–2.58)[a]
Haugen et al, 2008[9]	Norway	13,182[b]	European	0.22 (0.15–0.32)[b]
		2,864[c]		1.40 (1.02–1.92)[c]
Dafni et al, 1997[15]	Greece	837	European	0.60 (0.19–1.39)
Trontzas and Andrianakos, 2005[24]	Greece	10,647	AECG	0.15 (0.09–0.21)[d]
Alamanos et al, 2006[6]	Greece	488,435	AECG	0.09 (0.08–0.10)
Anagnostopoulos et al, 2010[14]	Greece	3,528	AECG	0.23 (0.22–0.75)
Bjerrum, 1997[10]	Denmark	499	European	0.6 up to 2.1
			Copenhagen	0.2 up to 0.8
Jacobsson et al,1989[11]	Sweden	705	Copenhagen	2.7 (1.0–4.5)

Notes: [a]3.2% ages <55 years; 5% ages >55 years; [b]ages 40–44 years; [c]ages 71–74 years; [d]0.08% ages 44–64 years; 0.40% ages >65 years.
Abbreviations: AECG, American–European consensus group; CI, confidence interval.

Mode d'entrée

Mode d'entrée			
Sécheresse	Parotidomégalie	Fatigue/Polyalgies	Signes extra-glandulaires

Bilan diagnostique

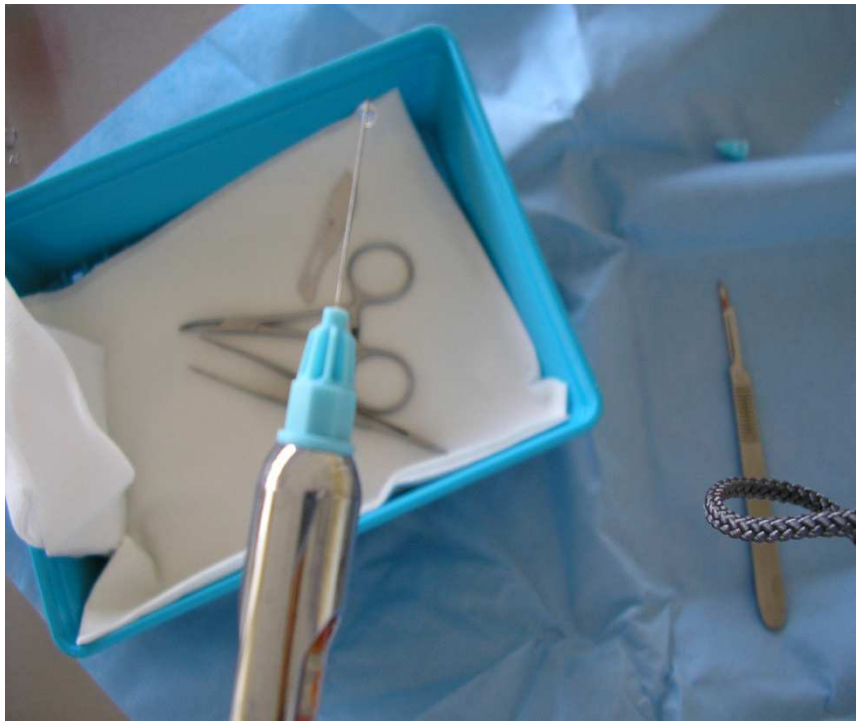
Principaux diagnostics différentiels		Diagnostic positif
Syndrome sec	Médicaments	Sécheresse buccale (question 1 des critères ***tableau I***) Sécheresse oculaire (question 2 des critères ***tableau I***) Flux salivaire Test de Shirmer Biopsies glandes salivaires Auto-anticorps (SSA-SSB) ± Echo glandes salivaires
Parotidomégalie	Lymphome Sarcoïdose	
Fatigue, polyalgies	Fibromyalgie Autres connectivités	
Signes extra-articulaires	Hépatite C VIH GVH	

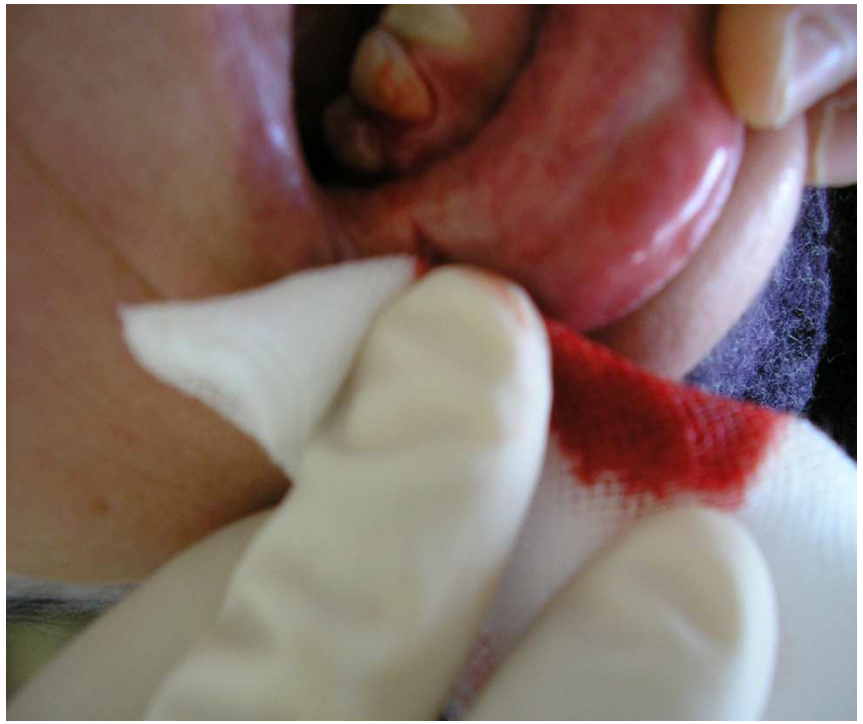
Symptômes oculaires
• Sensation quotidienne, persistante et gênante d'yeux secs depuis plus de 3 mois.
• Sensation fréquente de "sable dans les yeux".
• Utilisation de larmes artificielles plus de 3 fois par jour.
Symptômes buccaux
• Sensation quotidienne de bouche sèche depuis plus de 3 mois à l'âge adulte, glandes salivaires enflées de manière répétée ou persistante.
• Consommation fréquente de liquide pour avaler les aliments secs.
Signes cliniques ophtalmologiques
• Test de Shimer ≤ 5 mm/5 min.
• Score de Bijsterveld ≥ 4.
Histologie
• Infiltrat lymphocytaire (focus score ≥ 1, Chisholm ≥ 3).
Atteinte des glandes salivaires
• Scintigraphie salivaire.
• Scintigraphie parotidienne.
• Flux salivaire sans stimulation <1,5 mL/15 min.
Autoanticorps
• Anti-Ro (SS-A) ou anti-La (SS-B).
Critères d'exclusion
• Lymphome préexistant, SIDA, sarcoïdose, GVH.

Evaluation objective de la sécheresse Buccale

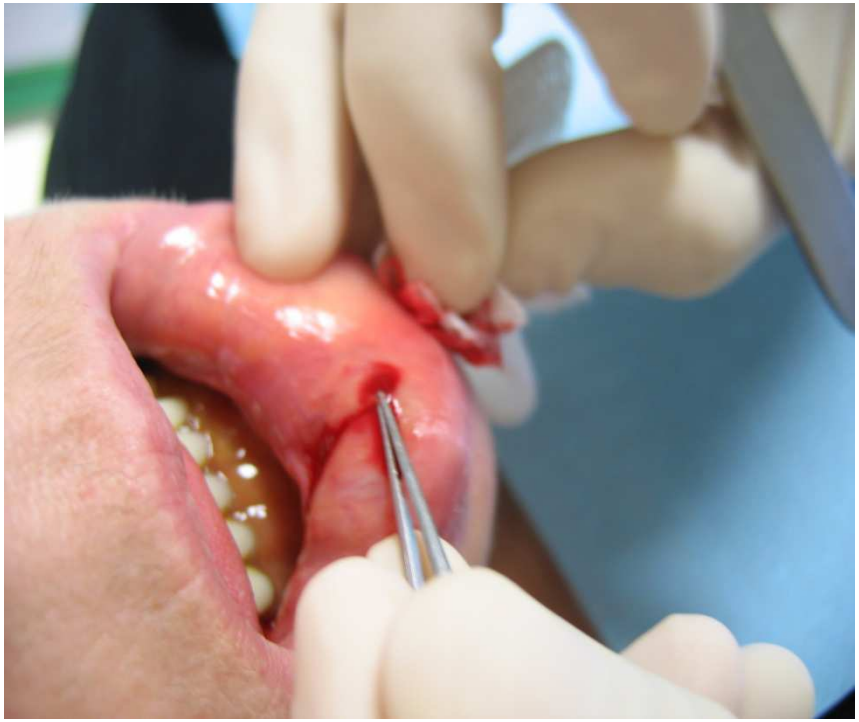
- Flux salivaire
  - Ni boire, ni manger et ni fumer une heure avant
  - Le matin entre 08h00 et 10h00.
  - Installé confortablement dans un fauteuil 5 minutes avant
  - Cracher toutes les minutes pendant 5 minutes dans un tube de centrifugation.
  - Echantillons pesés à l'aide d'une balance analytique.
  - L'élément d'analyse s'exprime en ml/min, le volume est déterminé selon la formule : l g = l ml.
  - Normal 0,1ml/min

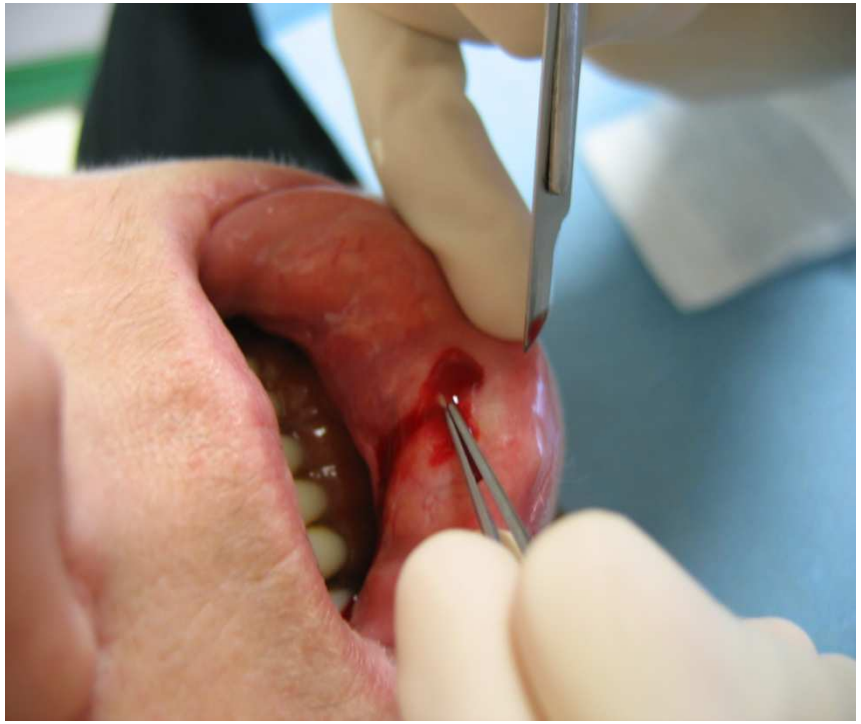
La biopsie de glande salivaire



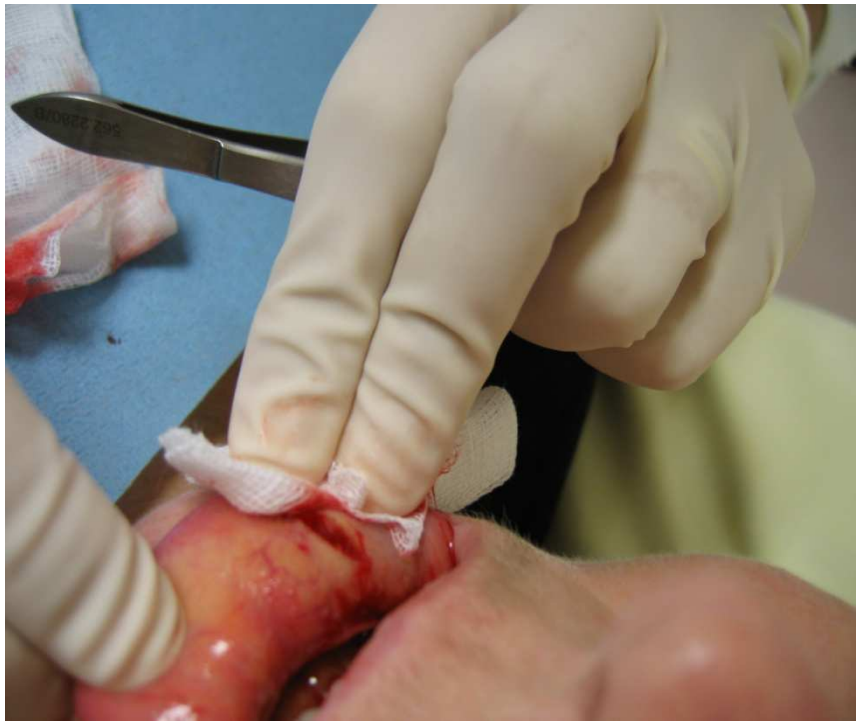


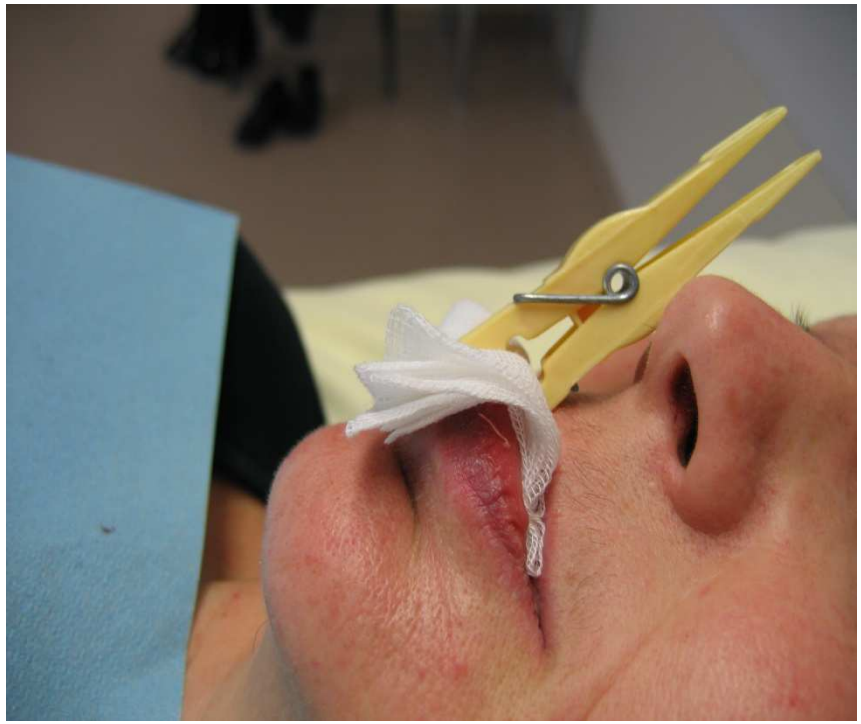
Technique





Technique





Interprétation

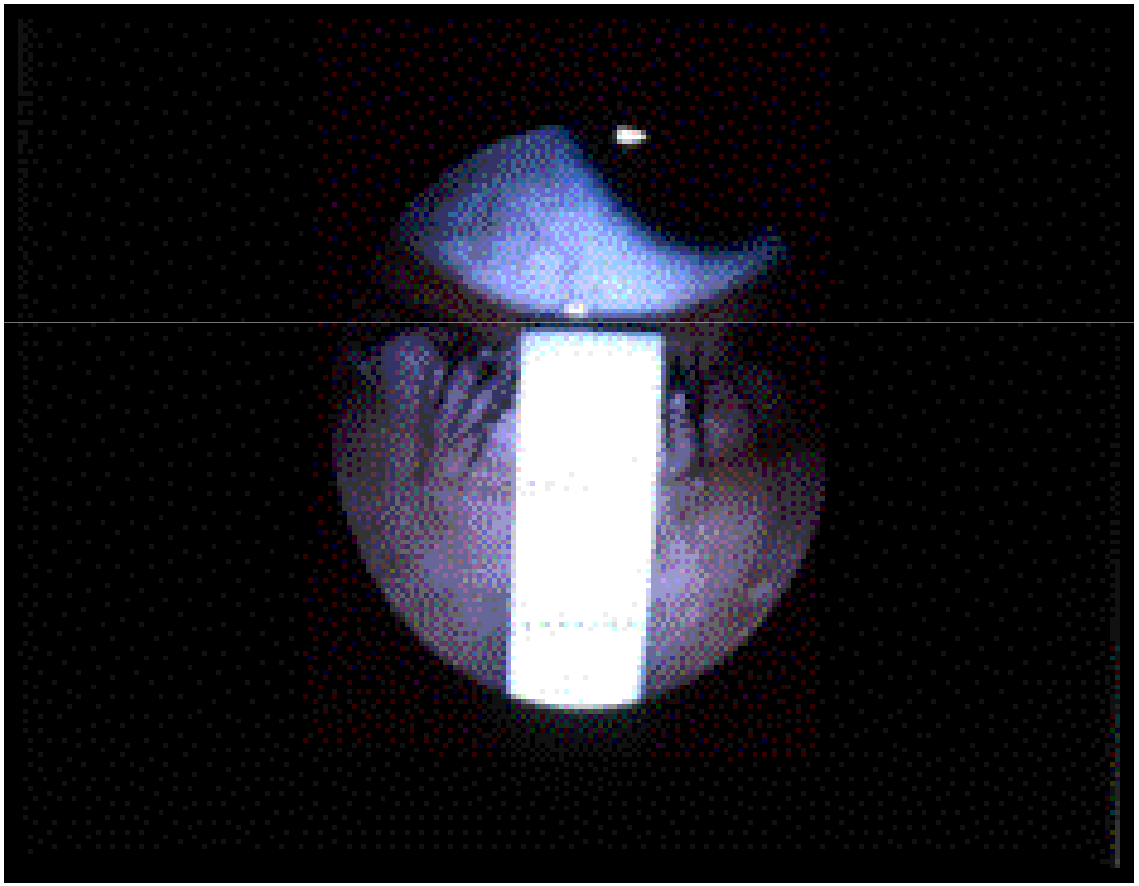
- **FOCUS SCORE ≥ 1**
  - Présence d'au moins un agglomérat de plus de 50 lymphocytes pour une surface glandulaire de 4 mm².
- **SCORE DE CHISHOLM ET MASSON (1968)**
  - **Grade 1 :** Discret infiltrat inflammatoire
  - **Grade 2 :** Infiltrat modéré ou < à un focus.
  - **Grade 3 :** 1 Focus (>50 lymphocytes) / 4mm2
  - **Grade 4 :** > 2 Foci/4mm2

Interprétation

- Variabilité par glande étudiée et par lecteur
- Etudes post mortem: 7 à 35% de Focus score >1 indépendamment de l'atrophie de la glande
- Focus score de stade 1 chez 3% des sujets jeunes de moins de 35 ans.

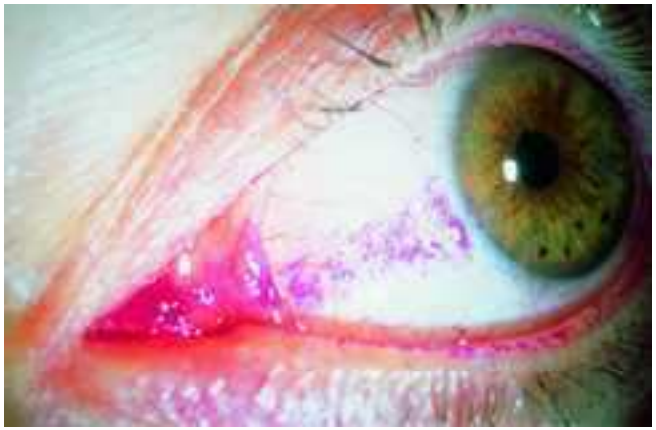
Al-Hashimi I, J Oral Pathol Med. 2001 Aug;30(7):408-12.
Takeda Y, J Oral Pathol. 1986 Feb;15(2):83-6.
Yarom N, Dayan D, Buchner A, Vered M. Oral Dis. 2007 May;13(3):274-8.

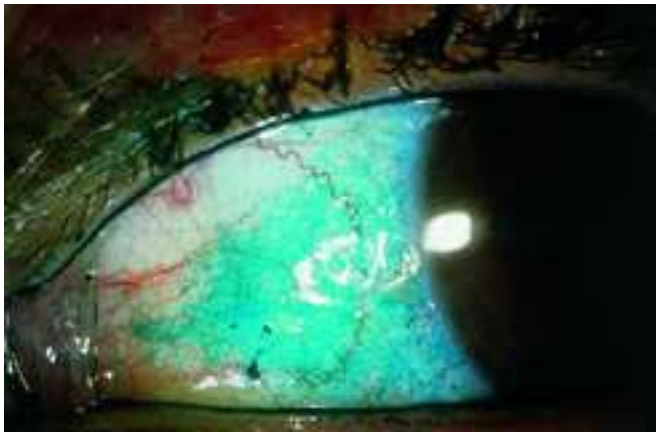
Test de Shirmer

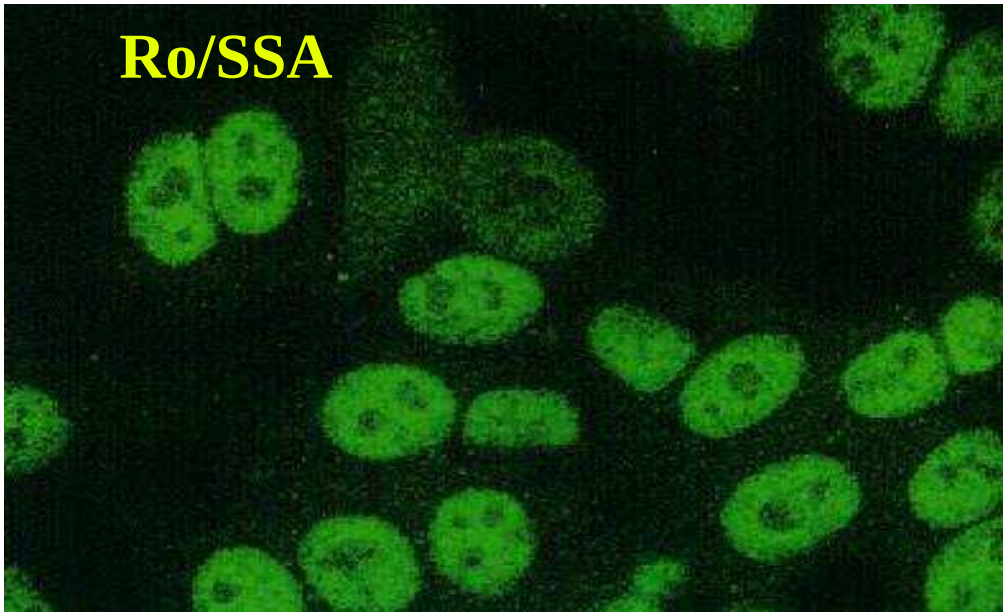


La stabilité du film lacrymal

- Le B.U.T (Beak up test): Instillation d'une goutte de fluorescéine puis observation à la lampe à fente avec un filtre bleu du film lacrymal. L'apparition de taches noires traduit la dessiccation et la rupture du film lacrymal. Le B.U.T. normal est supérieur à 25 secondes, l'anormal inférieur à 10 secondes.
- Les tests aux colorants vitaux: rose Bengale ou vert de Lissamine: Instillation d'une goutte dans le cul de sac conjonctival puis à laver. Le produit imprègne les cellules altérées.






Ro/SSA

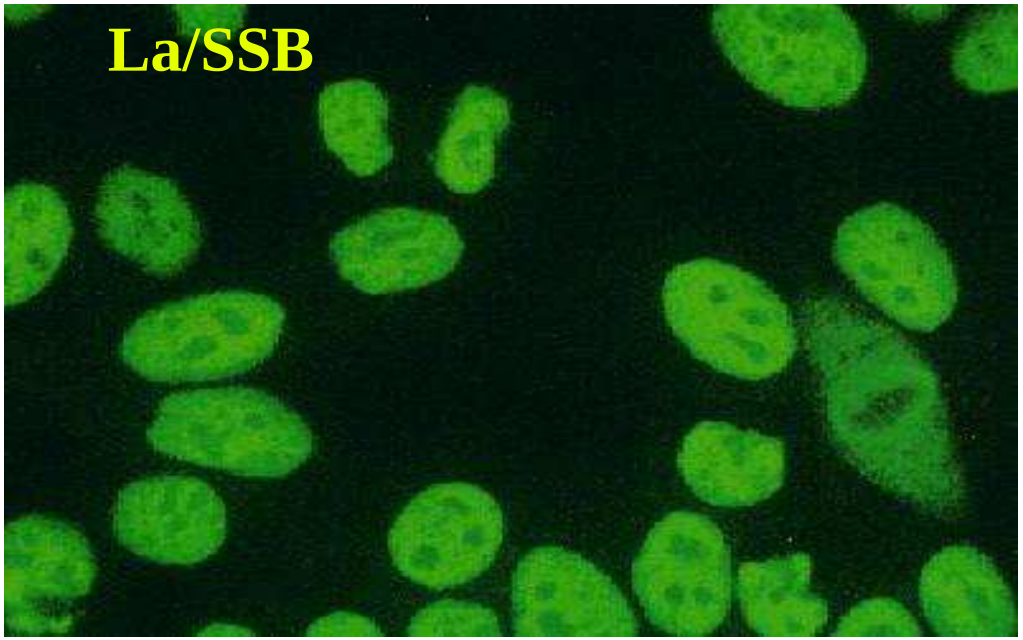

La/SSB

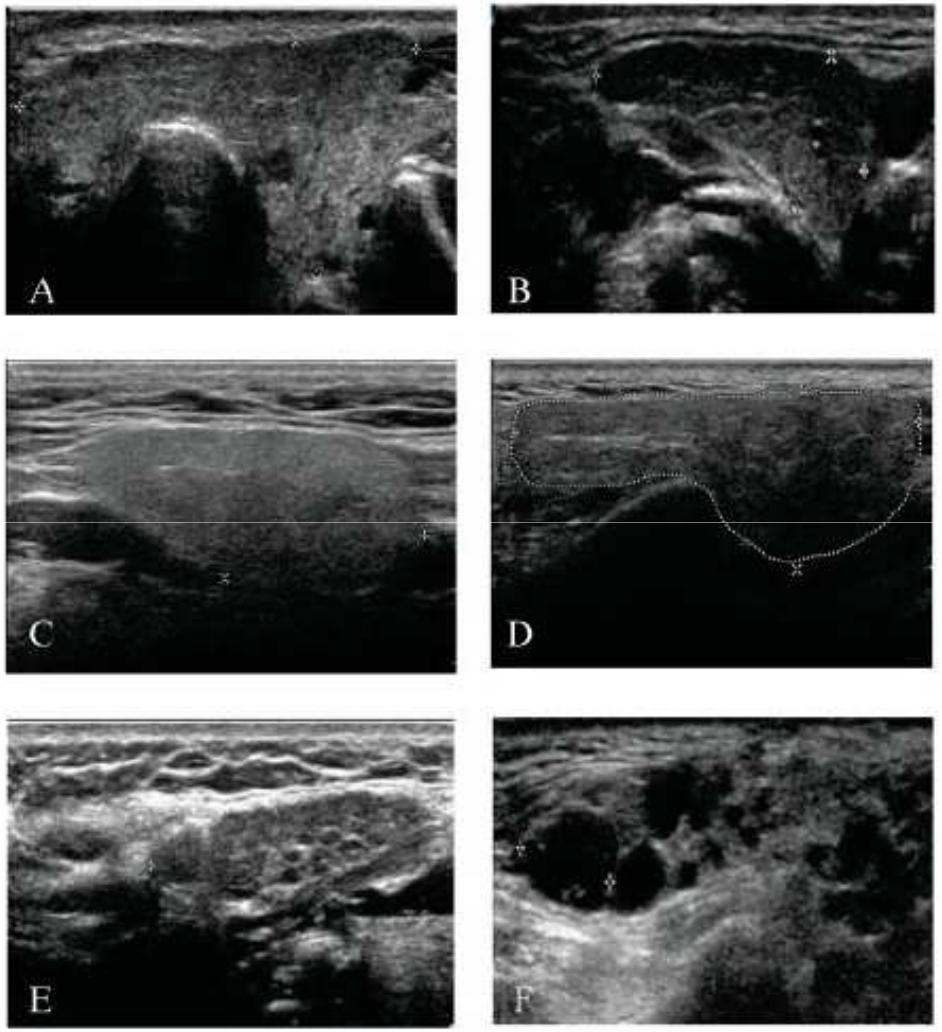
Table 3. Echostructure grade assessing parenchymal inhomogeneity of the major salivary glands in patients with and those without primary SS*

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

Table 4. Revised classification criteria for primary SS using a weighted score of 0–12.5*

Item	Points
Unstimulated salivary flow	
>0.1 ml/minute	0
≤0.1 ml/minute	1.5
Schirmer's test, 5 minutes	
>5 mm	0
≤5 mm	1.5
Labial salivary gland biopsy score†	
1–2	0
3–4	3
Anti-SSA or anti-SSB positivity	
No	0
Yes	4.5
Salivary gland ultrasonography grade	
0–1	0
2–4	2
Total	12.5

* A score of ≥5 of 12.5 had 85.7% sensitivity, 94.9% specificity, 94.4% positive predictive value, and 87.4% negative predictive value for the diagnosis of primary Sjögren's syndrome (SS).
† Determined using the system described by Chisholm and Mason (4).



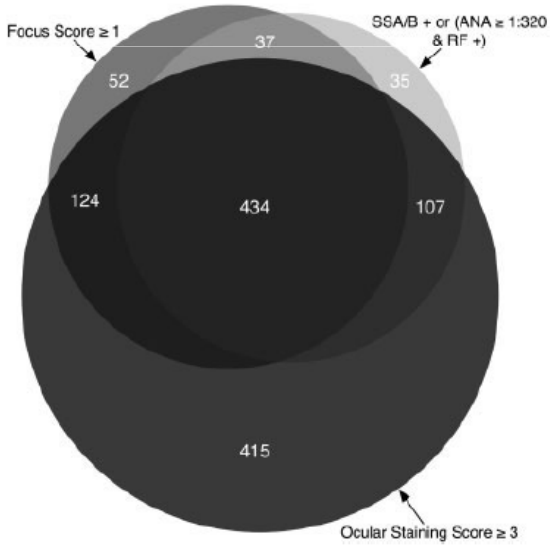
Cornec et al Arthritis 2013.

The classification of SS, which applies to individuals with signs/symptoms that may be suggestive of SS, will be met in patients who have at least 2 of the following 3 objective features:

1. Positive serum anti-SSA/Ro and/or anti-SSB/La or (positive rheumatoid factor and ANA titer ≥1:320)
2. Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥1 focus/4 mm^2†
3. Keratoconjunctivitis sicca with ocular staining score ≥3 (assuming that individual is not currently using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years)‡

Prior diagnosis of any of the following conditions would exclude participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests:

History of head and neck radiation treatment
Hepatitis C infection
Acquired immunodeficiency syndrome
Sarcoidosis
Amyloidosis
Graft versus host disease
IgG4-related disease



Shiboski et al Arthritis care 2013.

Critères d'évaluation

Bilan initial

Activité lymphocytaire B	Critères de mauvais pronostiques	Atteinte viscérale (ESSDAI)	Fatigue, sécheresse, douleur
Facteurs rhumatoïdes	Parotidomégalie	Pulmonaires	EVA fatigue, sécheresse et douleur
Ac anti-SS-A, SS-B	Polyadénopathie	Cutanées	
β2-microglobuline	Purpura	Parotidiennes	Consultation stomatologique
Electrophorèse des protéines plasmatiques	Vascularite	Neurologiques	Consultation ophtalmologique
Complément	Anémie	Articulaires	
Cryoglobulinémie	Lymphopénie	Pancréatique	
	C4 bas	Rénales	
	Cryoglobulinémie	Cytopénies	
		Musculaires	
		Adénopathies	
		Autres	

Selon ce bilan initial, la part d'activité et de séquelles

→ Traitement

→ Rythme de surveillance

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

4) How severe has your **mental fatigue** (not thinking clearly, finding it hard to concentrate, forgetting things, or making mistakes) been during the last 2 weeks?

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

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

1. Seror et al., ARD 2009

Domain [Weight]	Activity level	Description
Exclusion of weakness due to corticosteroids	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]	No = 0	Absence of currently active PNS involvement
Rate as "No activity" stable long-lasting features related to damage or PNS involvement not related to the disease	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]	No = 0	Absence of currently active CNS involvement
Rate as "No activity" stable long-lasting features related to damage or CNS involvement not related to the disease	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]	No = 0	Absence of auto-immune cytopenia
For anemia, neutropenia, and thrombopenia, only auto-immune cytopenia must be considered *Exclusion of vitamin or iron deficiency, drug-induced 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;

Traitements de la sécheresse

- Eviter
  - la fumée,
  - la sécheresse ambiante, le vent,
  - la lecture prolongée,
  - les médicaments
- Prendre des chewing gums ou bonbons sans sucre
- Salive artificielle en sprays : Aequasyal® : 1 pulvérisation endo-buccale à l'intérieur de chaque joue 3 à 4 X/J Artisial® , Syaline® ou Xialive® : 6 à 8 pullvérisations/jour
- Pour les candidoses buccales:
  - Fluconazole (Triflucan® solution): une cuillère mesure à 50 mg par jour pendant 1 à 2 semaines (à mélanger si besoin à des sirops sans sucre au choix)
  - Fungizone: en bain de bouche
  - bain de bouche bicarbonate à 1,4 %- 500m l+ PROCAINE 2%-10ml,
  - et/ou badigeonnage avec compresses de XYLOCAINE® visqueuse 1% (attendre 2 heures avant de manger ou boire) ou DYNEXAN® 2%.

Traitements de la sécheresse

- Larmes artificielles (Hydralarm®…), polymères visqueux (Lacrigel®, Dulcilarm®, Methylcellulose®…), gels de carbomères et acide hyaluronique (Vismed®) ou inserts (Lacrisert®).

- La ciclosporine localement.

- Dans les kératites ulcérées graves : Pommade à la vitamine A et fermeture de l'œil.

Traitements de la sécheresse

- Sialogogues
  - bromhexine (Bisolvon®) et anetholtrithione (Sulfarlem®)
    - non prouvé
  - chlorhydrate de pilocarpine
    - Salagen® 5mg 4 fois par jour
    - ou préparation magistrale de 4 mg 4 à 5 fois par jour,
    - Teinture de Jaborandi 10 à 30 gouttes trois fois par jour
  - la céviméline n'est pas commercialisée pour l'instant en Europe (Exovac® 90mg/j).

Traitements des signes généraux

- Antalgiques simples en privilégiant le paracétamol
- Les anti-inflammatoires sont quelquefois efficaces.
- La corticothérapie à petites doses (10 à 15 mg) en cure courte.
- Les benzodiazépines ou les antidépresseurs tricycliques (amitriptyline) à petite dose pour ne pas aggraver le syndrome sec

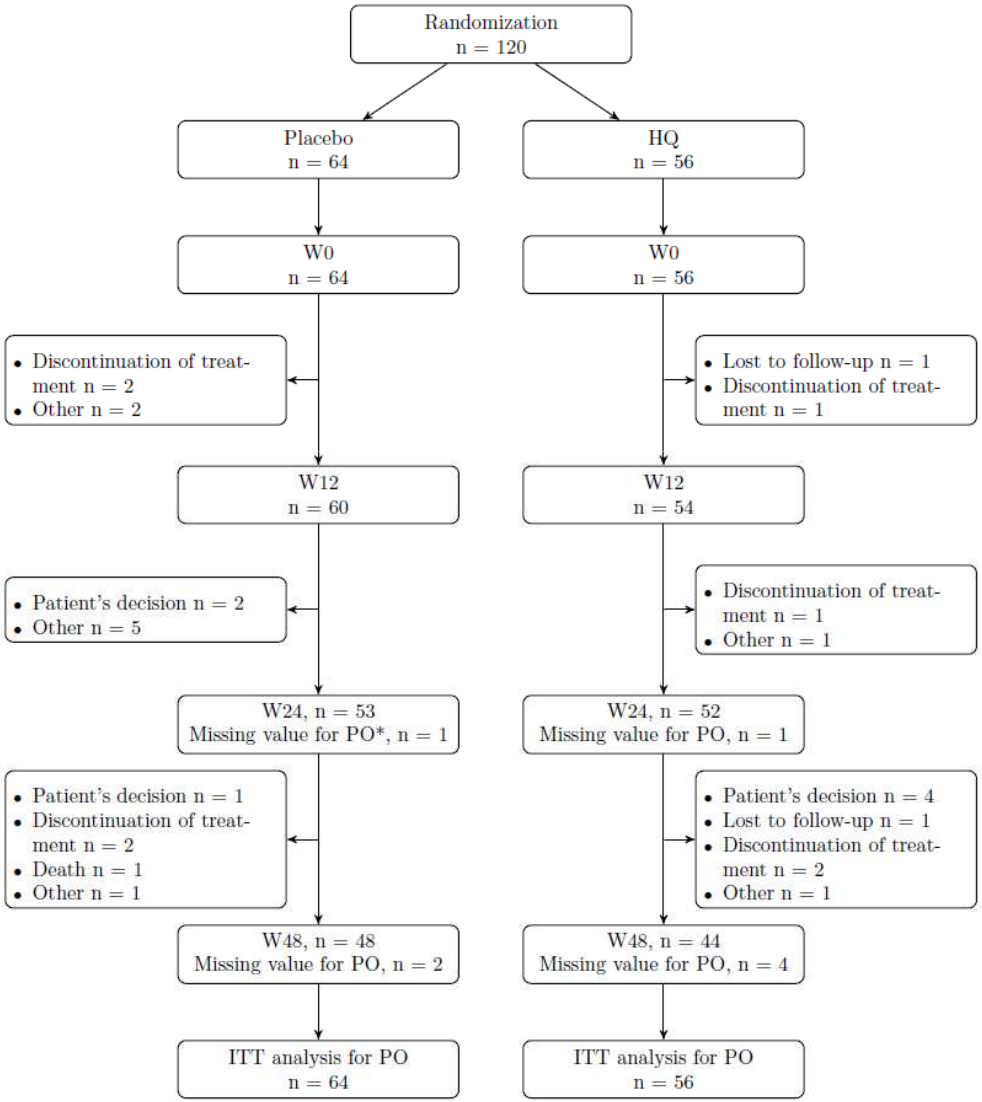
Traitements des signes viscéraux

- Complications neurologiques
  - Mononeuropathies multiples : corticothérapie initiale (0.5 à 1 mg/kg/jour), azathioprine ou cyclophosphamide
  - Neuropathies périphériques sensitives et sensitivo-motrices: Laroxyl®
  - Névralgie du trijumeau isolée: Laroxyl® ou corticothérapie faible dose.
- Vascularites du système nerveux central
  - Corticoïdes seuls ou en association avec azathioprine ou cyclophosphamide.
- Complications pulmonaires
  - Pneumonie interstitielle lymphoïde: corticothérapie (0.5 à 1 mg/kg/jour) ou en association à l'azathioprine
- Complications néphrologiques
  - néphropathie interstitielle lymphoïde: corticothérapie seule (1 mg/kg/jour) ou en association à un immunosuppresseur.

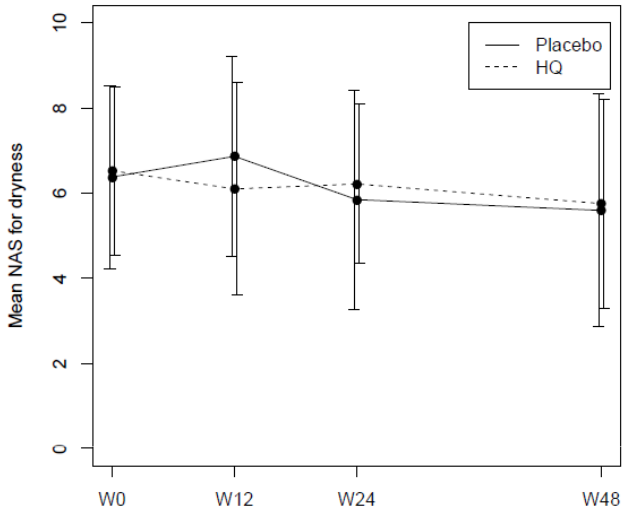
Traitements des signes viscéraux

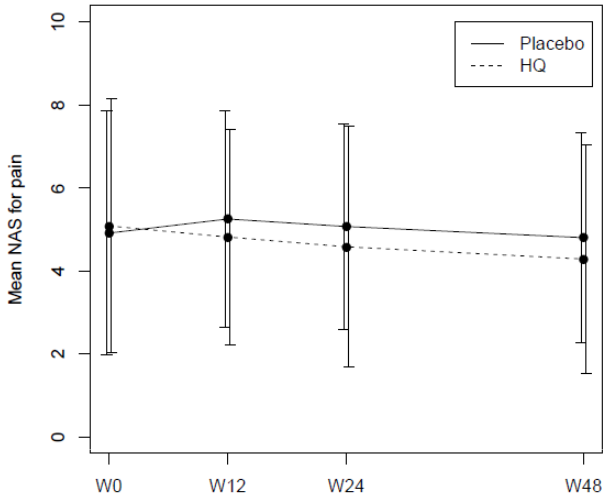
- Complications hématologiques
  - Lymphome : chimiothérapies ou radiothérapie seule.
  - Cytopénies auto-immunes: corticothérapie et/ou immunosuppresseur.
- Complications cutanées :
  - Erythème polymorphe, vascularites, purpura: corticoïdes.
- Complications articulaires (synovites)
  - Méthotrexate ou le léflunomide
- Parotidomégalie
  - Elle doit faire rechercher un lymphome.
  - Elle peut être traitée au coup par coup par corticoïdes (de l'ordre de ¼ à ½ mg/kg) lorsqu'elle évolue par courte crise,
  - mais dans les formes chroniques on évoque de plus en plus la possibilité de traitement par Rituximab
  - De ce fait la chirurgie est le plus souvent évitée.

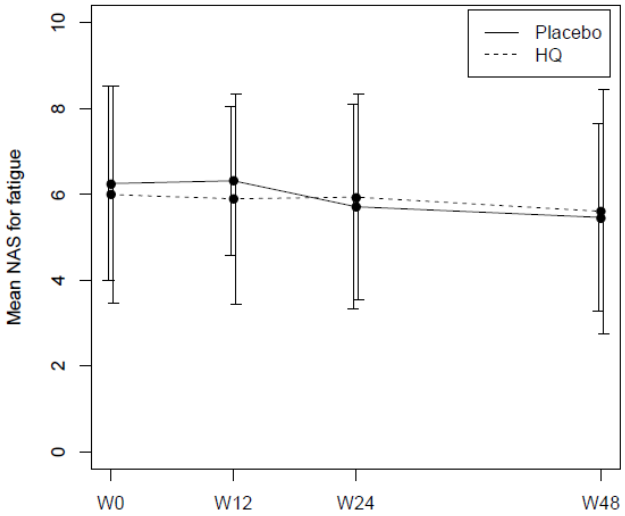
Etude JOQUER

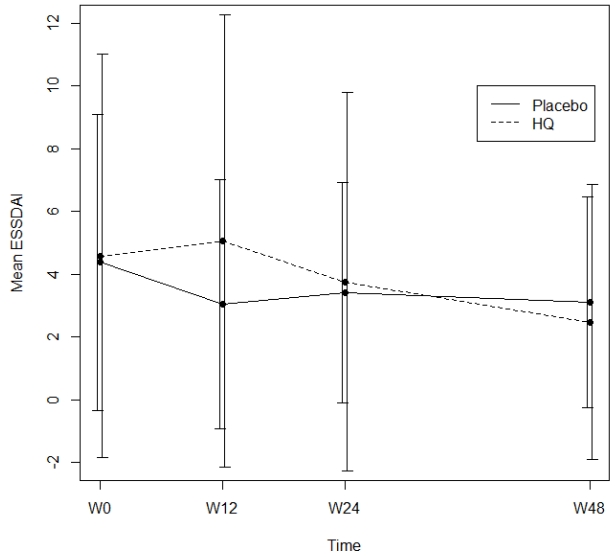


Etude JOQUER









Essais ouverts

Reference	Medicament	N	Objectif
Steinfeld et al., 2001	Infliximab	16	30% EVA oeil, bouche, fatigue et VS
Zandbelt et al., 2004	Etanercept	15	questionnaire MFI, VAS, flux, Schirmer, Rose Bengale, BUT, SGB
Pijpe et al., 2005	Rituximab	15	VAS, flux, Schirmer, Rose Bengale, BUT, SGB
Steinfeld et al., 2006	Epratuzumab	16	≥20% 2/4: Schirmer, flux, VAS fatigue, VS+/- IgG
Devauchelle-Pensec et al., 2007	Rituximab	16	VAS, flux, Schirmer, Rose Bengale, BUT, SGB, SF-36 et SGUS
Mariette et al., 2015 BELISS	Belimumab	30	≥30% 2/5 response VAS fatigue, sécheresse douleur, VAS activité médecin, marqueurs B
al., 2013	Rituximab	12	Tolérance, activité clinique et biologique
2014	Abatacept	15	ESSDAI, ESSPRI

Essais double aveugle

Reference	Medicament	N	Objectif
Sankar et al., 2004	Etanercept	14	≥20% 2/3 domains: sécheresse oeil et bouche, VS et Ig
Mariette et al., 2004 TRIPPS	Infliximab	103	≥30% 2 /3 VASs douleur, fatigue, sécheresse
Dass et al., 2008	Rituximab	17	20% VAS fatigue
Meijer et al., 2010	Rituximab	30	Flux salivaire
TEARS 2014	Rituximab	120	30-mm 2/4 VASs
TRACTISS 2014	Rituximab	110	30% VAS fatigue et sécheresse
ETAP	Tocilizumab	120	ESSDAI amélioration ≥3 points versus baseline

Etanercept et Sjogren

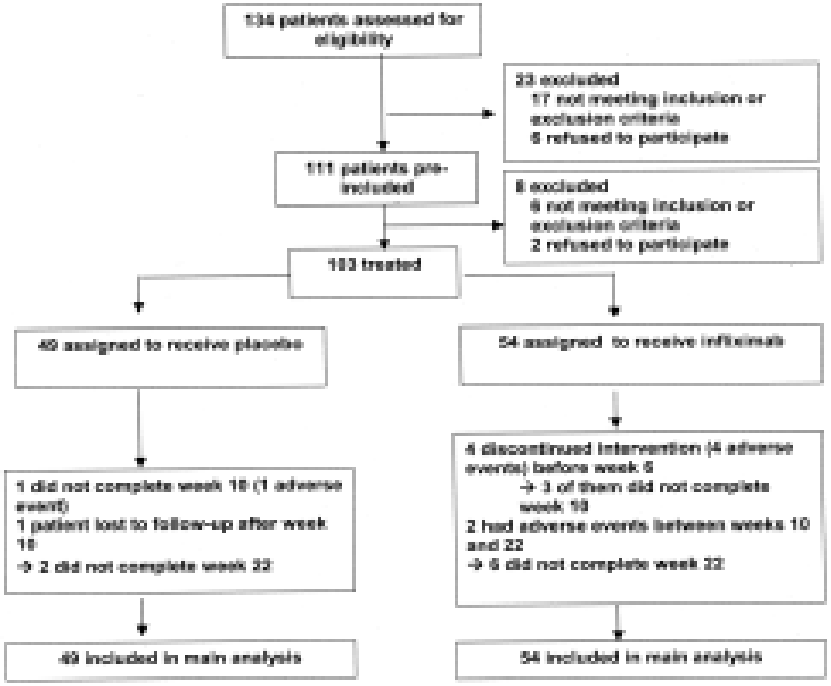
12 weeks vs inclusion

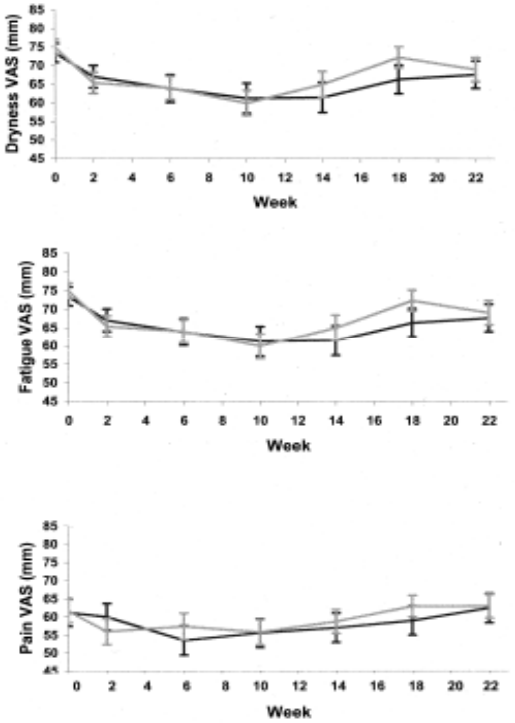
	Etanercept (n = 14)	Placebo (n = 14)	*P*
Dry mouth, by 100-mm VAS	−2 (−13, 2)	3 (−11, 10)	0.44
Dry eyes, by 100-mm VAS	1 (−6, 12)	−0.5 (−13, 5)	0.53
Schirmer I test, mm/5 minutes	−0.75 (−1.5, 1.00)	−0.50 (−2, 0)	0.55
Van Bijsterveld score	0 (−1.5, 0.5)	−0.25 (−1, 0)	0.96
Total stimulated saliva flow, 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

No evidence to suggest that treatment was clinically efficacious in SS.

Sankar V. Arthritis Rheum. 2004. 2240-2245

Infliximab et Sjogren





anti-TNF agent did not show any evidence of efficacy of infliximab in pSS.

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

Réduction de la fatigue dans le sjogren primitif traité par Rituximab

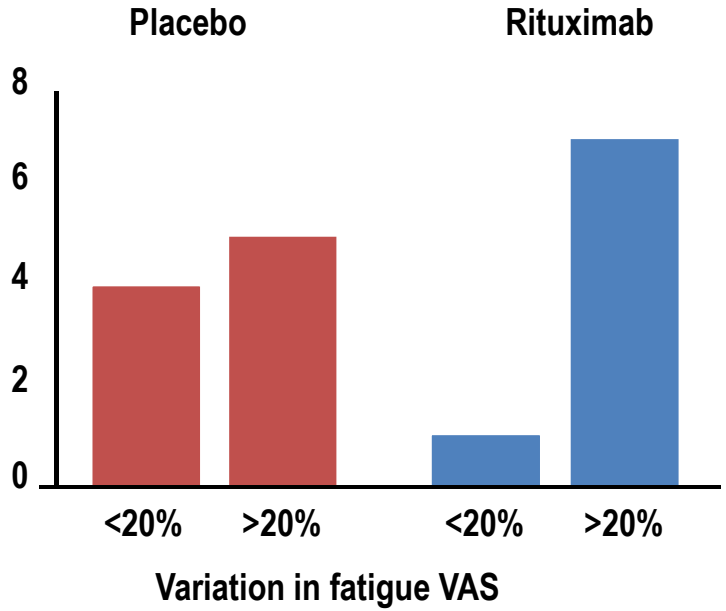
- SS primitif (AECG, anti-Ro/La, fatigue>50/100)
- Rituximab: 1000 mg J1 et J 14 vs placebo
- methylprednisolone 100 mg +prednisolone 60 mg/j, J 2–7 puis 30 mg/j, J 8–14
- Critère principal: 20% réduction EVA fatigue à 6 mois

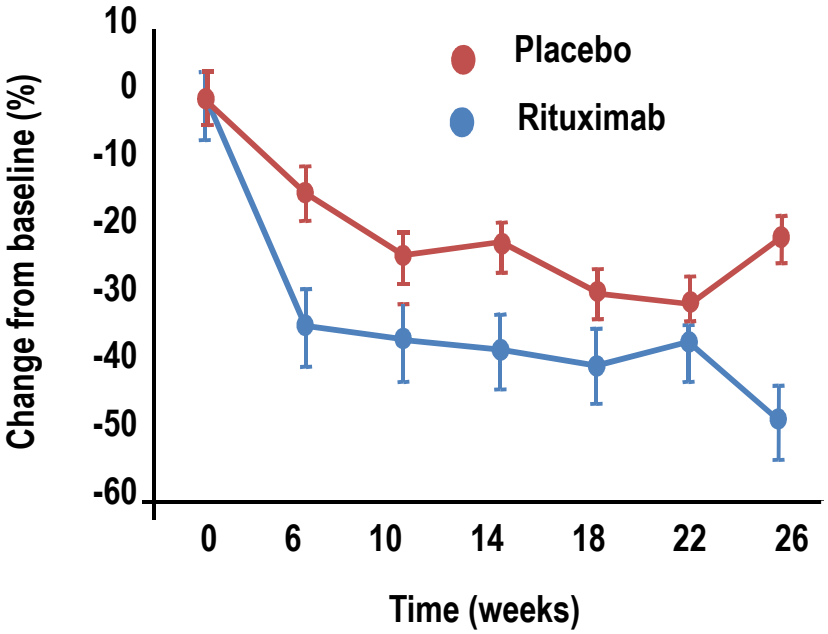
	RTX	Placebo
Patients (n)	8	9
Age (ans)	51 (22–64)	54 (41–64)
Durée de la maladie (ans)	7.25 (1–18)	8.25 (2–19)
EVA fatigue (mm)	76 (61–95)	69 (53–99)
Anti-SSA (%)	100	100
Anti-SSB (%)	78	67
IgG (U/mL)	18.61	20.98

Dass et al, Ann Rheum Dis, 2008: 67(11):1541-4.

Réduction de la fatigue dans le sjogren primitif traité par Rituximab

- Resultats
  - Pas de différence sur le critère principal
  - Réduction de la fatigue vs inclusion dans le groupe rituximab (p=0.001)





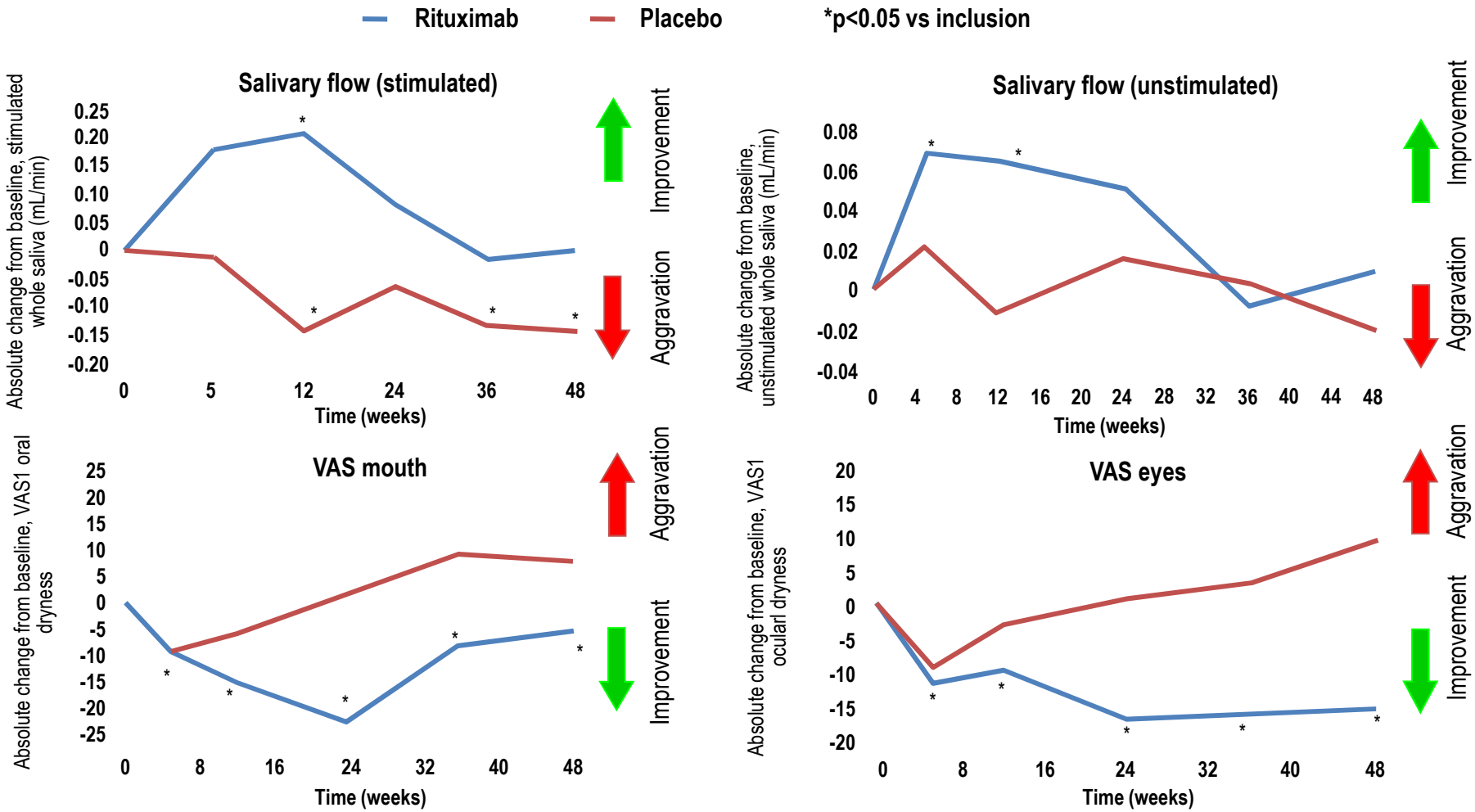
Dass et al, Ann Rheum Dis, 2008: 67(11):1541-4.

Traitement par Rituximab dans le sjogren primitif

- Essai randomisé rituximab vs placebo dans le syndrome de Sjögren
- Inclusion
  - n=30 (AECG)
  - Age: 43 ans
  - Durée de la maladie (moyenne): 67 mois
    - Flux salivaire estimulé (>0.15 mL/min
    - Anti-SSB ou anti-SSA et RF
    - SGLB grade III ou IV
  - 2 perfusions de 1000 mg de rituximab/placebo J0 et J15
  - Ctritère principal: Flux salivaire stimulé à 12 semaines

Meijer et al, arthritis rheum 2010;62(4):960-8.

Traitement par Rituximab dans le sjogren primitif



Meijer et al, arthritis rheum 2010;62(4):960-8.

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

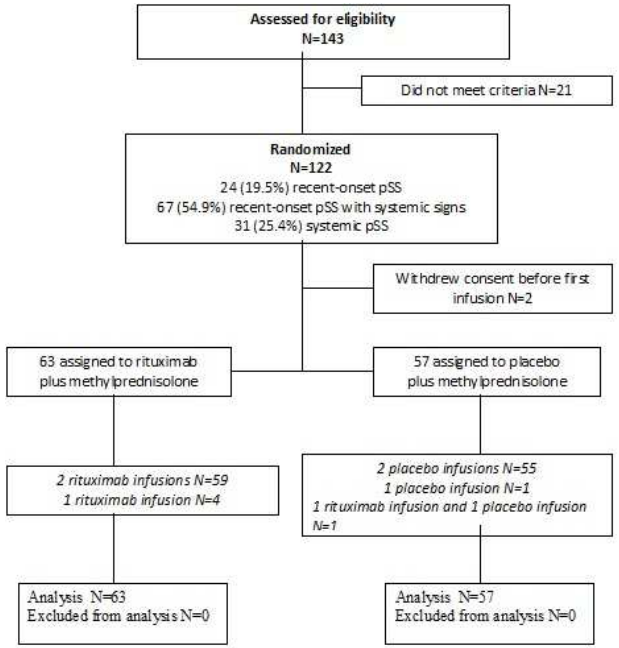
For author affiliations, see end of text.

Annals of Internal Medicine | ORIGINAL RESEARCH

Treatment of Primary Sjögren Syndrome With Rituximab

A Randomized Trial

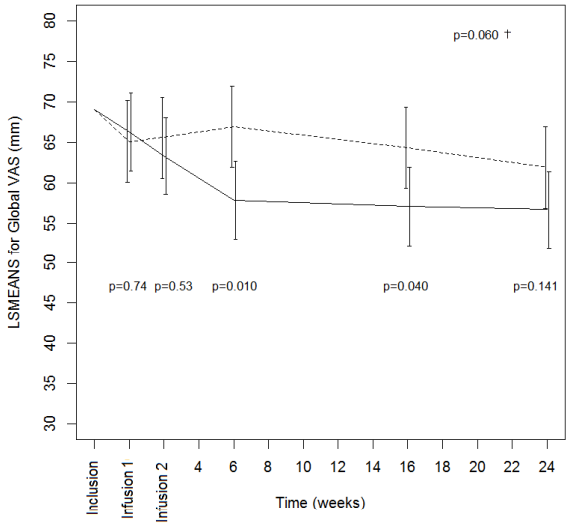
Valérie Devauchelle-Pensec, MD, PhD; Xavier Mariette, MD, PhD; Sandrine Jousse-Joulin, MD; Jean-Marie Berthelot, MD; Aleth Perdriger, MD, PhD; Xavier Puéchal, MD, PhD; Véronique Le Guern, MD, PhD; Jean Sibilia, MD, PhD; Jacques-Eric Gottenberg, MD, PhD; Laurent Chiche, MD, PhD; Eric Hachulla, MD, PhD; 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

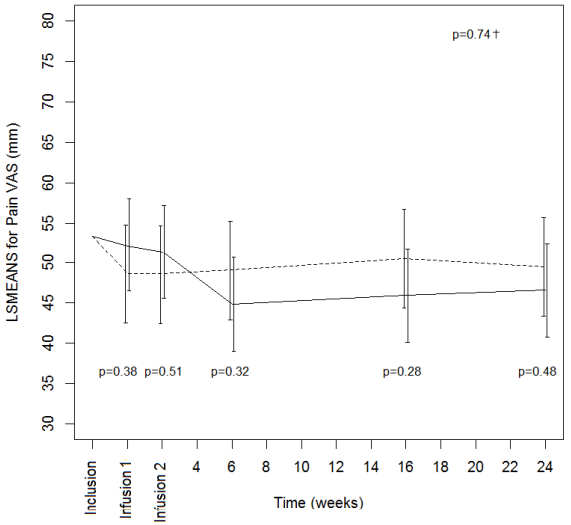


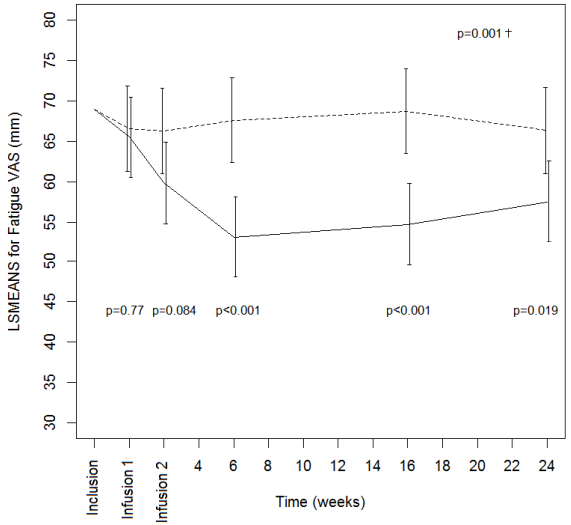
Variable	Week 6			
	Rituximab	Placebo	Difference (95% CI)	*P* Value
Patients with ≥ 30-mm improvement in VAS score, %†				
≥ 2 of 4 VASs‡	22.4	9.1	13.3 (0.8 to 25.8)	0.036
Global	15.8	8.0	7.8 (−8.6 to 24.1)	0.35
Pain	18.0	14.0	3.9 (−9.9 to 17.8)	0.57
Fatigue	34.7	8.2	26.6 (15.7 to 37.5)	<0.001
Dryness	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

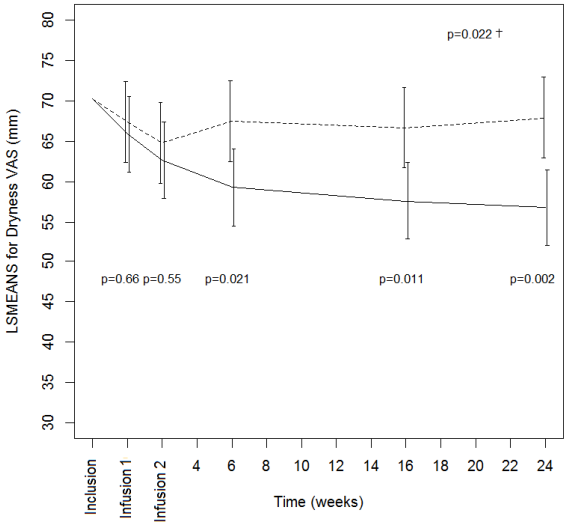
Week 16				Week 24			
Rituximab	Placebo	Difference (95% CI)	*P* Value	Rituximab	Placebo	Difference (95% CI)	*P* Value
26.3	17.0	9.3 (−1.5 to 20.0)	0.091	23.0	22.0	1.0 (−16.7 to 18.7)	0.91
20.5	18.2	2.4 (−11.2 to 16.0)	0.73	16.9	24.0	−7.1 (−19.1 to 4.9)	0.25
15.2	15.9	−0.7 (−8.6 to 7.2)	0.86	12.6	22.0	−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


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


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


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


LSMEANS for Dryness VAS (mm)
p=0.022 †
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)

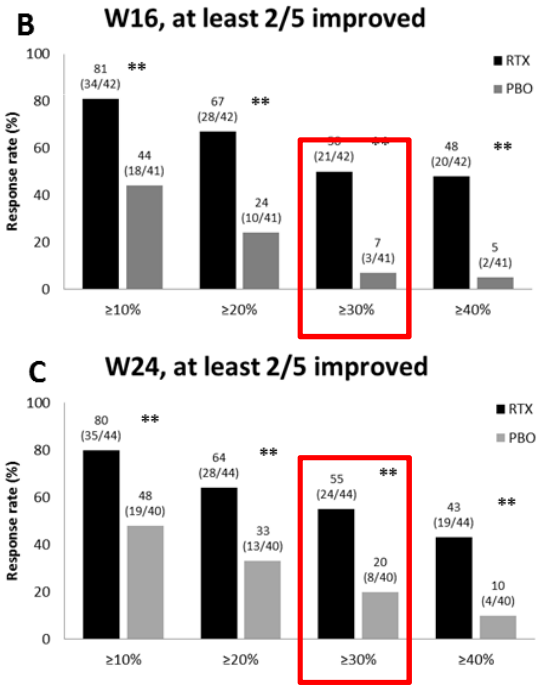
FATIGUE (RTX)
0
20
40
60
80
100
Inclusion
Infusion 1
Infusion 2
6
10
14
18
22
Time (weeks)

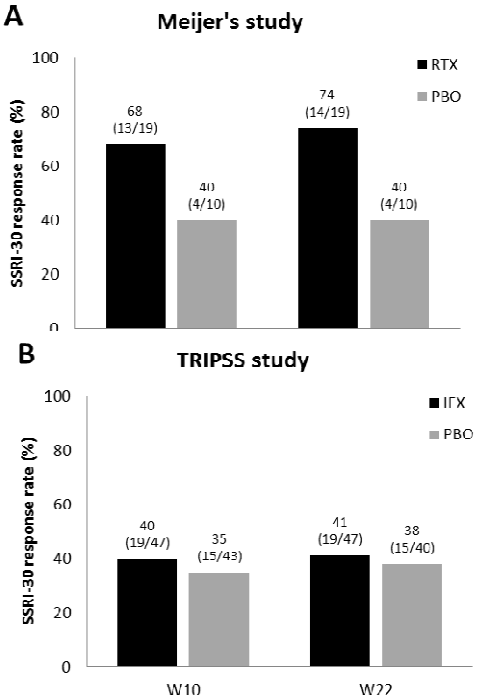
FATIGUE (PBO)
0
20
40
60
80
100
Inclusion
Infusion 1
Infusion 2
6
10
14
18
22
Time (weeks)

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

Sjögren's Syndrome Responder Index (SSRI)

- « Core set » :
  - VAS sécheresse orale
  - VAS sécheresse oculaire
  - VAS Fatigue
  - Flux
  - VS
- SSRI-30: ≥30% 2/5





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

Etudes prévues

Etude	médicament	Promoteur	N	Objectif
NCT01552681	Baminercept, Lymphotoxin-beta Receptor Fusion Prot	National Institute of Allergy and Infectious Diseases	72	Flux
NCT02291029	CFZ 533, anti-CD40 monoclonal Ab	Novartis	30	ESSDAI
NCT02334306	AMG 557/MEDI587, anti-ICOS-L monoclonal Ab	MedImmune/ Amgen	42	ESSDAI
NCT01782235 ETAP	Tocilizumab Phase 3	Université Strasbourg	110	ESSDAI
NCT02149420	*VAY 736*, anti-BAFF-R mAb	Novartis	30	ESSDAI
NCT02067910	Abatacept Phase 3	Gröningen and BMS	88	ESSDAI

Conclusion

- Des patients
  - Ayant une mauvaise qualité de vie
  - Peu améliorés par les traitements symptomatiques
- Des progrès notables
  - Sur le diagnostic
  - Sur la notion d'activité-séquelle
  - Sur le rôle des lymphocytes B
- Des essais thérapeutiques
  - Sur le lymphocyte B (TEARS, TRACTISS)
  - avec le plaquenil (Joquer)
  - Avec l'anti IL6 actuellement
  - Avec des anti CD22, petites molécules…demain