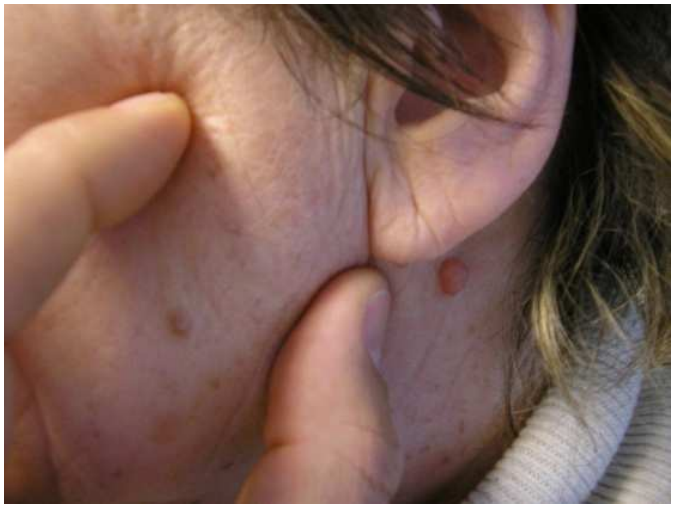
Traitement du syndrome de Sjögren en 2013



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Evaluer les conséquences biologiques et radiologiques

- Biologie
  - VS, CRP
  - NFS
  - BH, ionogramme, créatinine, NEFU, protéinurie
  - Electrophorèse+/-dosage pondéral et IEP
  - C4, CH50
  - cryoglobulinémie
  - FAN et spécificité
  - FR
  - B2 microglobuline
- Imagerie
  - Radiographie pulmonaire initiale et si symptôme

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;

Pronostic

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

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

→ Traitement

→ Rythme de surveillance

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
- Des substituts de larmes et de salive
- 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 aussi
  - 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,
    - 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

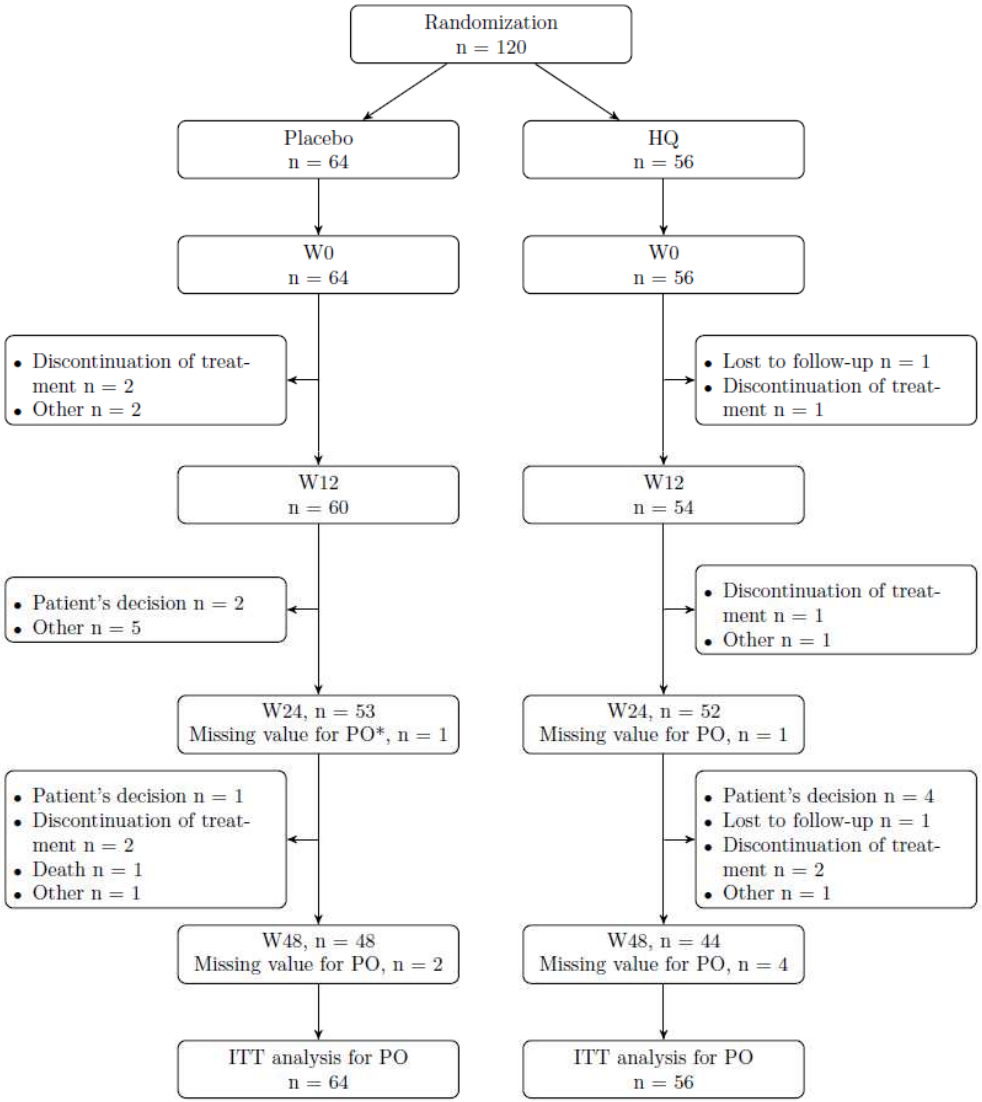
Traitements des signes viscéraux

- 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.

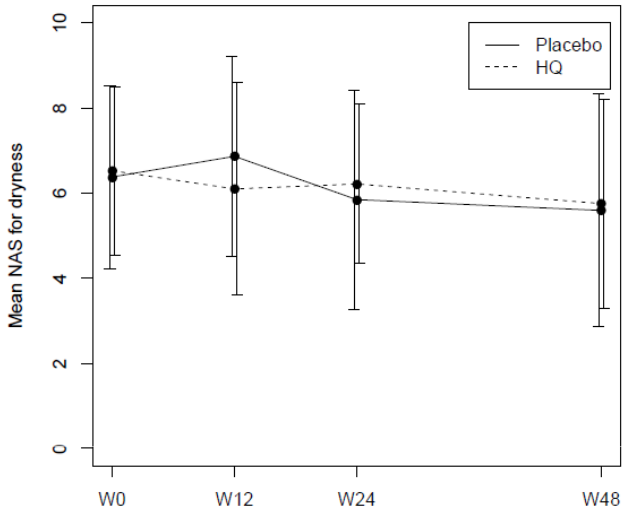
Traitements des signes viscéraux

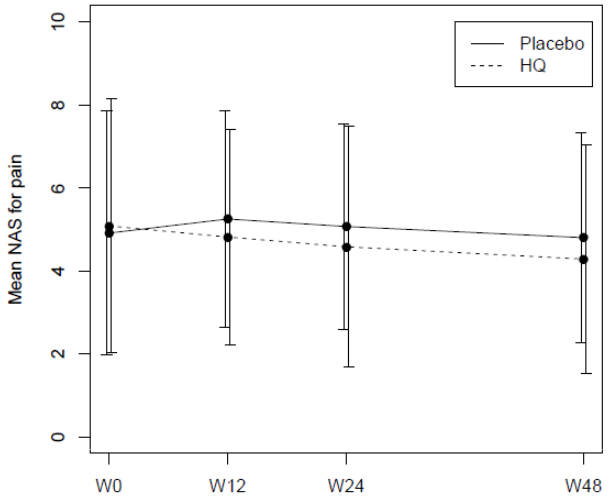
- Complications hématologiques
  - Lymphome : chimiothérapies ou radiothérapie seule.
  - Cytopénies auto-immunes: corticothérapie et/ou immunosuppresseur.
- Complications cutanées :
  - Erythème polymorphe, vascularites, purpura: corticoïdes.
- Complications articulaires (synovites)
  - Méthotrexate 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.

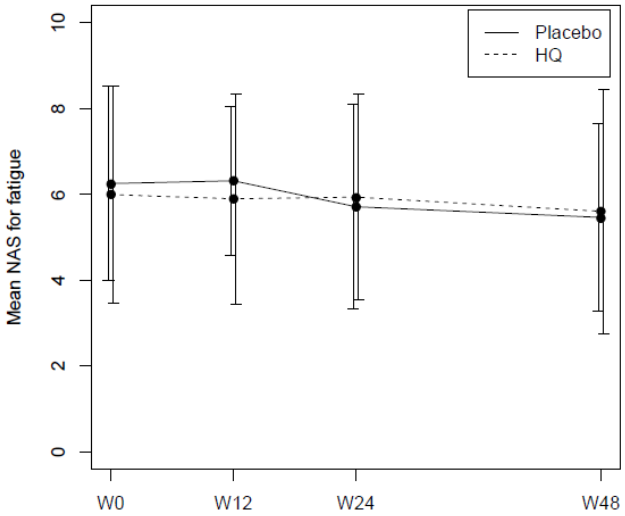
Etude JOQUER

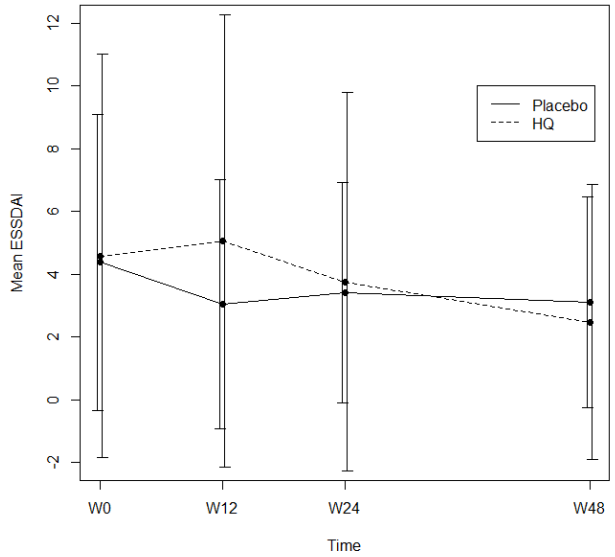


Etude JOQUER









Trials Evaluating Biologic Agents.

Table 3. Trials Evaluating Biologic Agents

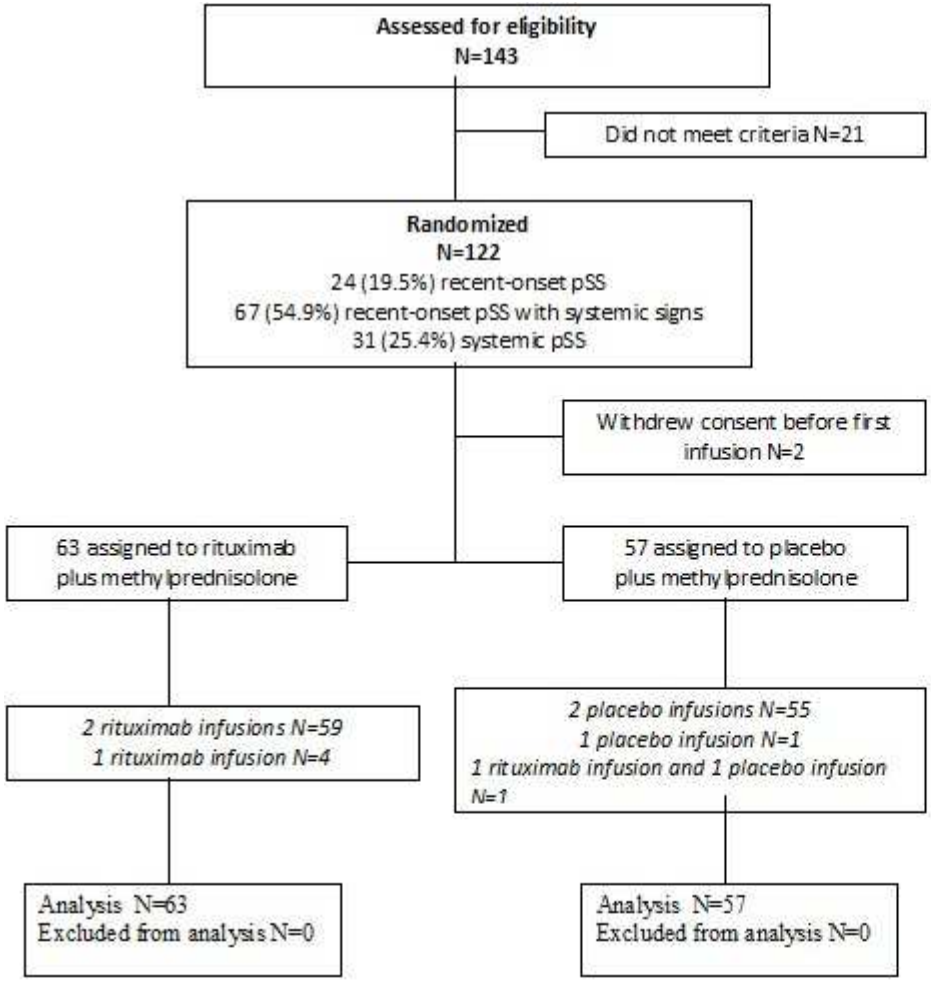
Source	No. (F, No.)	Study Design (Duration)	Drug (Patients, No.)	Control (Patients, No.)	Results	Adverse Events
Mariette et al,[32] 2004	103 (NA)	RCT-d (22 wk)	Infliximab 5 mg/kg (n = 54) wk 0, 2, 6	Placebo (n = 49)	Primary outcome (vs placebo): % of patients with favorable response (17% vs 20%, $P = .62$). Secondary outcomes (vs placebo): patients with ≥30% decrease in pain VAS (20% vs 26%, $P = .46$), fatigue VAS (24% vs 24%, $P = .96$), and dryness VAS (17% vs 16%, $P = .96$); change in salivary flow rate, mL/min (0.03 vs 0.02, $P = .24$), Schirmer test, mm (0.9 vs 1.5, $P = .75$), swollen joint count (–0.4 vs –0.3, $P = .75$), tender joint count (–2.4 vs –2.3, $P = .97$), ESR, mm/h (–0.8 vs –0.9, $P = .97$), CRP, mg/L (–0.4 vs –0.5, $P = .96$), gamma globulins, g/L (0.78 vs 0.13, $P = .05$), IgG, g/L (0.74 vs 0.03, $P = .24$), IgA, g/L (0.16 vs 0.09, $P = .56$), and IgM, g/L (0.34 vs 0.04, $P = .001$).	Total vs placebo: 11% vs 2% ($P = .11$); infliximab: 2 infusion reactions, 1 lupus-like rash, 1 autoimmune hepatitis, 1 pneumococcal septicemia, 1 breast cancer; placebo: 1 polyclonal lymph node enlargement
Meijer et al,[33] 2010	30 (29)	RCT-d (48 wk)	Rituximab 1 g/15 d (n = 20) wk 0 and 2	Placebo (n = 10)	Primary outcome (vs placebo): increased stimulated whole saliva, mL/min (0.66 vs 0.28, NS). Secondary outcomes (vs placebo): increased unstimulated whole saliva, mL/min (0.18 vs 0.05, NS), Schirmer test score, mm/5 min (10 vs 5, NS), lysamine green score (2 vs 4, NS), tear break-up time, sec (6 vs 4, NS), IgM-R, U/L (103 vs 225, NS), MFI general fatigue score (15 vs 14, NS), SF-36 total score (55 vs 62, NS), oral dryness VAS (50 vs 69, NS), dry eyes VAS (46 vs 76, $P < .05$).	Total vs placebo: NA; total infections vs placebo: 55% vs 40% ($P = .43$); 12 infections in 11 rituximab patients, 7 infections in 4 placebo patients
Sankar et al,[34] 2004	28 (26)	RCT-d (12 wk)	Etanercept 25 mg (n = 14) twice per wk	Placebo (n = 14)	Primary outcome (vs placebo): % of patients with favorable response (36% vs 21%, $P = .20$). Secondary outcomes (vs placebo): change in dry mouth VAS (–2 vs 3, $P = .44$), dry eyes VAS (1 vs –0.5, $P = .53$), salivary flow rate, mL/min (–0.03 vs –0.22, $P = .63$), Schirmer test, mm/5 min (–0.75 vs –0.5, $P = .55$), van Bijsterveld score (0 vs –0.25, $P = .96$), IgG, mg/dL (10 vs –30, $P = .82$), and ESR, mm/h (–5.5 vs 1.5, $P = .004$).	Total vs placebo: 14% vs 7% ($P = .50$); AE etanercept: 1 atypical injection-site reaction, 1 rapidly enlarging skin lesion; AE placebo: upper respiratory infection
Dass et al,[35] 2008	17 (NA)	RCT-d (6 mo)	Rituximab 1 g/15 d (n = 8) wk 0 and 2	Placebo (n = 9)	Primary outcome (vs placebo): patients with >20% improvement in fatigue VAS (87% vs 56%, $P = .36$). Secondary outcomes (vs placebo): social functioning SF-36 score (12 vs –25, $P = .01$), mental health SF-36 score (4 vs –24, $P = .06$), PROFAD differences NA, RF reduction (45 vs 0, $P = .05$), immunoglobulin levels (NS), Schirmer test, salivary flow rate (NS).	3 serious AE in 2 patients (delayed reaction with meningism, probable gastroenteritis, palpitations), 2 additional infusion reactions

Abbreviations: AE, adverse events; CRP, C-reactive protein; ESR, erythrosedimentation rate; F, female; MFI, Multidimensional Fatigue Inventory; NA, not available; NS, no significant differences; PROFAD, Profile of Fatigue and Discomfort; RCT-d, double-blind randomized controlled trial; RF, rheumatoid factor; SF-36, 36-Item Short Form Health Survey; VAS, visual analog scale.

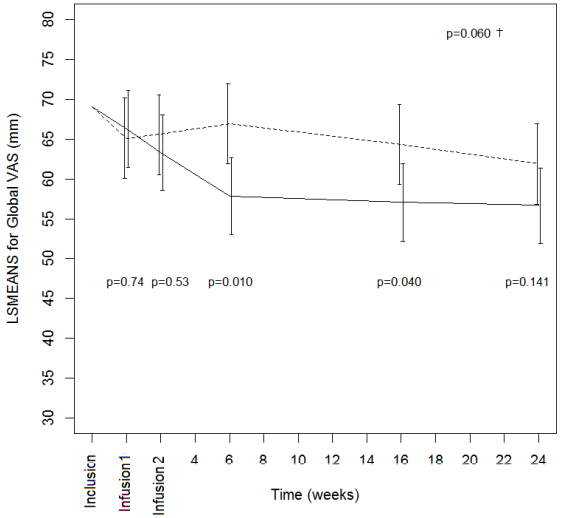
Ramos-Casals, M. et al. JAMA 2010;304:452-460

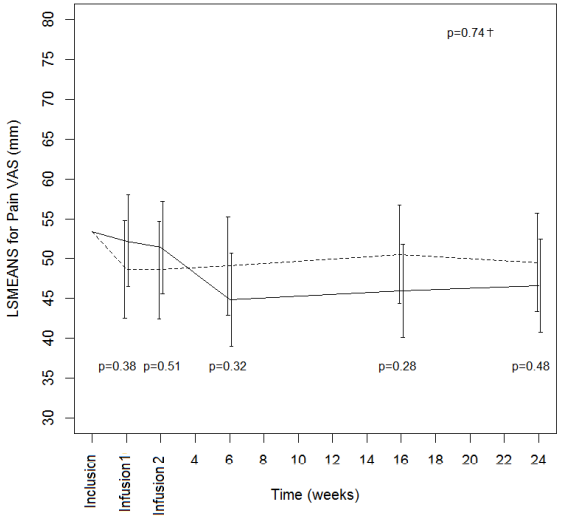
JAMA

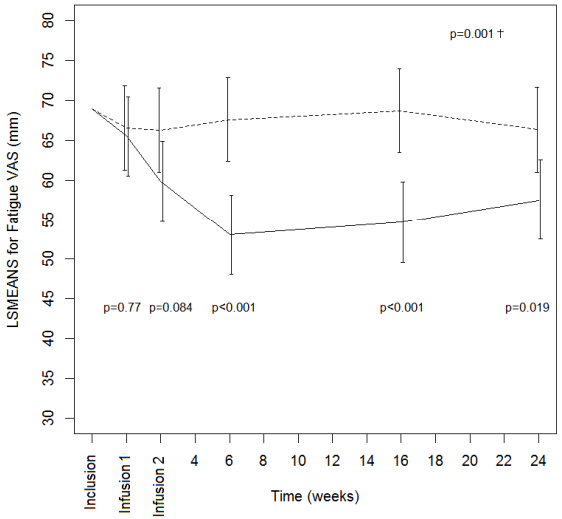

TEARS

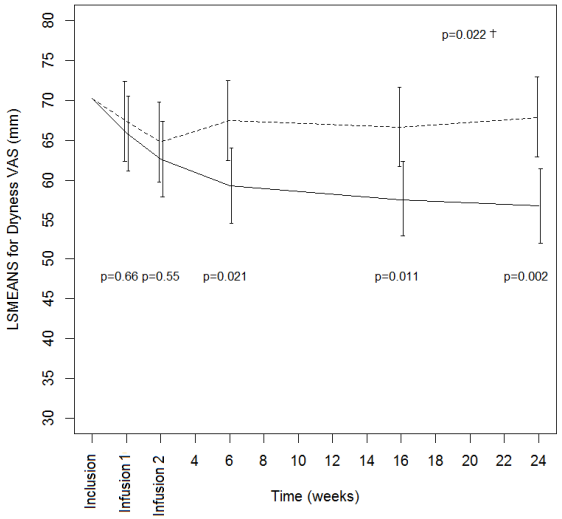

Assessed for eligibility
N=143
Did not meet criteria N=21
Randomized
N=122
24 (19.5%) recent-onset pSS
67 (54.9%) recent-onset pSS with systemic signs
31 (25.4%) systemic pSS
Withdrew consent before first infusion N=2
63 assigned to rituximab plus methylprednisolone
57 assigned to placebo plus methylprednisolone
2 rituximab infusions N=59
1 rituximab infusion N=4
2 placebo infusions N=55
1 placebo infusion N=1
1 rituximab infusion and 1 placebo infusion N=1
Analysis N=63
Excluded from analysis N=0
Analysis N=57
Excluded from analysis N=0

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)

Etudes à venir

- Leflunomide

- Epratuzumab (anti CD22)
- Tocilizumab (ETAP) si ESSDAI≥8
- Petites molécules (anti JAK)