Advances in diagnosis and management of Sjögren's Syndrome

HỘI NGHỊ KHOA HỌC THƯỜNG NIÊN 2025

15 tháng 03 năm 2025

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Sjögren syndrome

Systemic autoimmune disease
Exocrin gland dysfunction (sicca)

Female Sex ratio 9Female/1male
50 years old

« **primary**" if it is not associated with "**secondary**"
an underlying autoimmune disease
Rheumatoid arthritis, SLE or systemic sclerosis

Extraglandular manifestation

Extraglandular and articular manifestation :25-30%

Cryoglobulinemic vasculitis

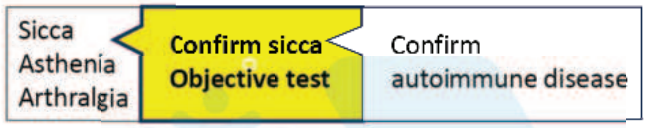
B lymphoma
2-5% of patients

Diagnosis

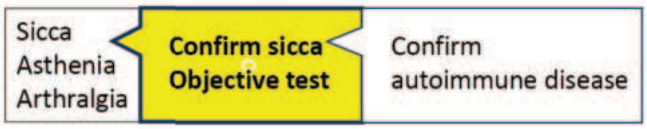
Sicca Asthenia Arthralgia	Confirm sicca Objective test	Confirm autoimmune disease

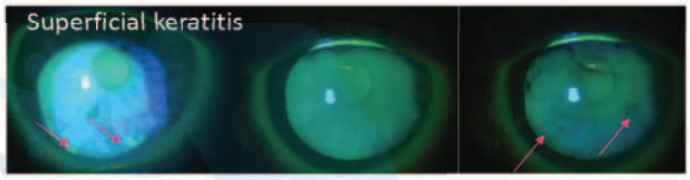
Sicca Asthenia Arthralgia	**Differential diagnosis Many causes of sicca** **Medications** (eg, antidepressants, anticholinergics, beta-blockers, diuretics, antihistamines, some antiarrhythmic and antiepileptic drugs)/ **chemotherapy** Anxiety and depression **Chronic disease** (eg diabete, hepatitis C, sarcoidosis...) Age dehydratation **Local etiology** (eg Complications from contact lenses) Dehydration Environmental irritants Therapeutic radiation or surgery to the head and neck .....

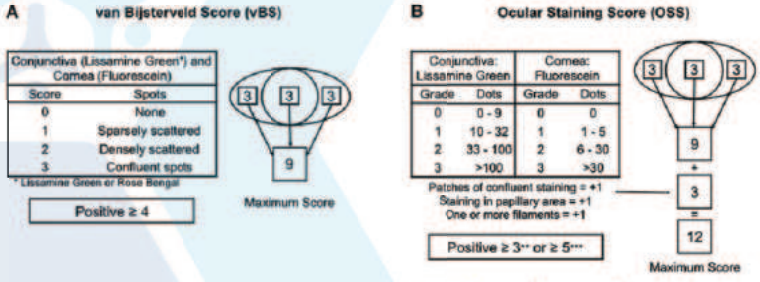
Diagnosis



Diagnosis



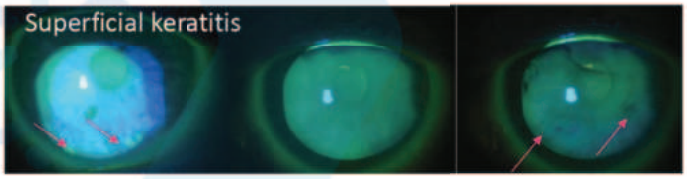




SICCA Ocular staining score. Total scores of 0 to 12 per eye assess the range of severity for dry eye.

Diagnosis

Sicca Asthenia Arthralgia	**Confirm sicca** **Objective test**	Confirm autoimmune disease



A van Bijsterveld Score (vBS)

Conjunctiva (Lissamine Green*) and Cornea (Fluorescein)	
Score	Spots
0	None
1	Sparsely scattered
2	Densely scattered
3	Confluent spots

* Lissamine Green or Rose Bengal

Positive ≥ 4

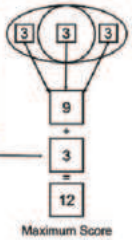
Maximum Score

B Ocular Staining Score (OSS)

Conjunctiva: Lissamine Green		Cornea: Fluorescein	
Grade	Dots	Grade	Dots
0	0 - 9	0	0
1	10 - 32	1	1 - 5
2	33 - 100	2	6 - 30
3	>100	3	>30

Patches of confluent staining = +1
Staining in papillary area = +1
One or more filaments = +1

Positive ≥ 3** or ≥ 5***

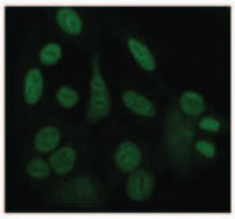


Maximum Score

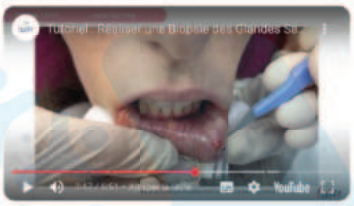
SICCA Ocular staining score. Total scores of 0 to 12 per eye assess the range of severity for dry eye.

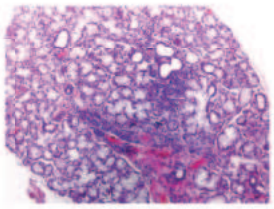
Sjögren syndrome
Diagnosis

Sicca Asthenia Arthralgia	Confirm sicca Objective test	**Confirm** **Autoimmune** **disease**



https://youtu.be/M4s1UUsQmKY



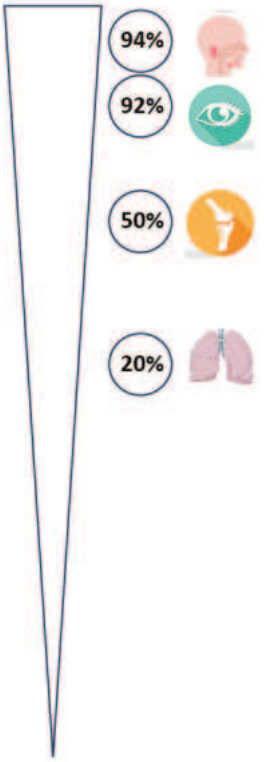


Item	Weight score
Labial salivary gland with focal lymphocytic sialadenitis and focus score ≥ 1	3
Anti-SSA (Ro) +	3
Ocular staining score ≥ 5 (or van Bijsterfeld score ≥ 4) on at least one eye	1
Schirmer ≤ 5 mm/5min on at least one eye	1
Unstimulated whole saliva flow rate ≤ 0.1 ml/min	1

ACR-EULAR Classification Criteria for primary Sjögren's syndrome — **score ≥ 4**

Shiboski *et al.* Ann Rheum Did 2017

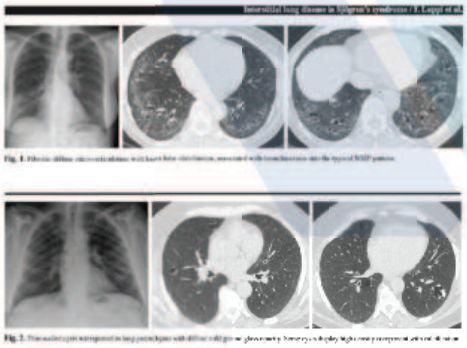
Systemic disease



SICCA syndrome

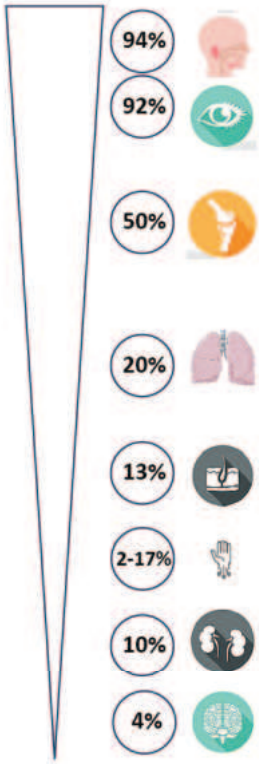
Arthralgia or non erosive arthritis

Interstitial Lung Disease - brochiectasies- kystic lesion



Luppi F *et al.* Clin Exp Rheumatol. 2020

Systemic disease



SICCA syndrome

Arthralgia or non erosive arthritis

ESSDAI

Interstitial Lung Disease - brochiectasies- kystic lesion

Cutaneous vasculitis - erytheme annulaire

Pure sensory neuropathies and axonal sensorimotor polyneuropathies-cranial nerve. Small fiber-ganglionopathy

Tubulointerstitial nephritis 75% / glomerulonephritis : cryoglobulinemic vasculitis

focal or multifocal lesions, multiple sclerosis-like disease, and isolated optic neuritis

EULAR Sjögren's syndrome (SS) disease activity index (ESSDAI)

12 domains/ each domain have a **Weight** (from 1 to 5)
Absence 0 / Low 1 / moderate 2 /high 3 Activity
Multiply acitivity degre by the weight of the domain

Constitutionial (fever, sweats, body lost) 0/1/2 x3			**Lymphadenopathy Lymphoma** 0/1/2/3 x4	
Glandular 0/1/2 x2	**Articular** 0/1/2/3 x2	**cutaneaous** 0/1/2/3 x3	**Pulmonary** 0/1/2/3 x5	**Renal** 0-3 x5
Muscular 0/1/2/3 x6	**Peripheral nervous system** 0/1/2/3 x5		**Central nervous system** 0/2/3 x5	
Hematological 0/1/2/3 x2	**Biological** (C3 C4 CH50, gammoglobuline, cryo) 0/1/2 x1			

Seror R *et al.* ESSDAI. RMD open 2015

EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI)

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

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

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

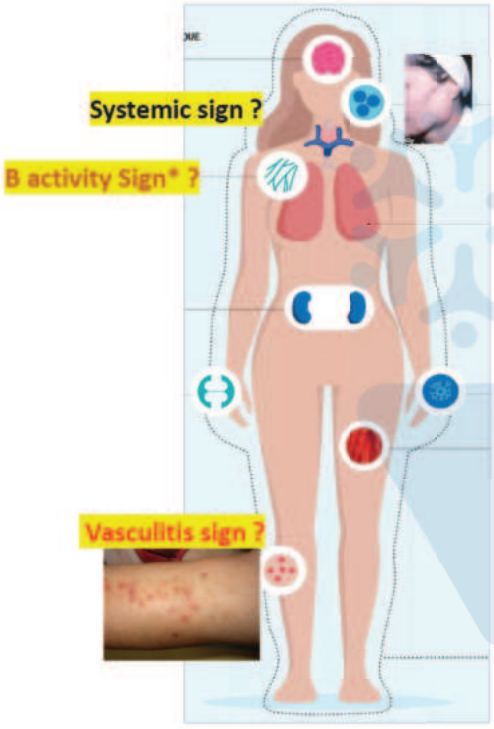
No fatigue	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10	Maximal imaginable fatigue

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

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

Seror R *et al.* Ann Rheum Dis 2011

Follow up



Signs of activity on the ESSDAI score :
Every 3 to 6 months

Quiescent or mildly phenotypic forms :
Once a year or every 2 years

During pregnancy :
Every 1 to 3 months especially if anti-SSA/SSB antibodies +

French national and diagnosis and care protocol. 2022

Follow up

At each visit

Cell blood count /platelets
Blood ionogram, creatinine levels and glomerular filtration rate
CRP
Proteinuria/creatinuria ratio on sample
Albuminemia, liver function tests alkaline phosphatases
CPK.

Protein electrophoresis (every 6 months *)
Rheumatoid factor (every 6 months*)
C3, C4 (Every 6 months*)
Cryoglobulinemia (Every 6 months*)

Initial and before pregnancy
Antiphospholipid markers

At least once a year

French national and diagnosis and care protocol. 2022

Predictive factor for lymphoma

RisK **x10**

5%
MALT
B Lymphoma

- Clinical evidence of salivary gland enlargement
- Clinical evidence of lymphadenopathy
- Low C3/C4 with low C4 being the strongest predictor
- Rheumatoid factor
- Cryoglobulinaemia
- Monoclonal gammopathy
- Lymphopenia
- High focus score (>4)
- ESSDAI . Activity of disease

Nocturne G *et al*. Arthritis Rheumatol 2016
Salvator *et al*. Expert Rev Clin Immunol
Chatziz LG *et al*. Rheumatology 2022
Chatzis L *et al*. J autoimmun

Predictive factor for lymphoma

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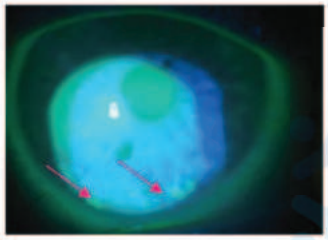
Immunofixation
LDH
B2 Microglobuline

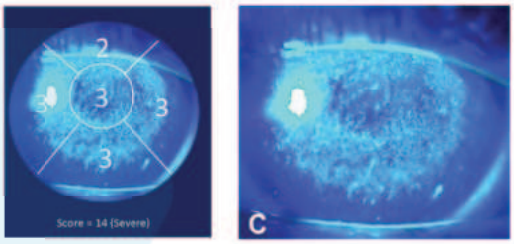
PET-Scan
if difficult access : Cervico-thoraco-abdomino-pelvic **CT scan**

Parotid ultrasound if asymmetric/persistent parotidomgaly
A **new BGSA** : lymphoma?
especially if persistant parotid or submandibular hypertrophy
If the BGSA has not revealed lymphoma
a parotid biopsy in the case of a **parotid nodule**

lymph node biopsy and/or mass biopsy

Ocular Dryness- Treatement





Artificial tears + Ointment
viscosity agent
hyaluronate

Topical Glucocorticoides

Topical ciclosporine

Serum eye drops

Oral muscarinic agonist

Picture from Alejandro Rodriguez-Garcia *et al*. Clin Ophtalmol 2022

Ramos- Casals M *et al*. Ann Rheum Dis 2020

Oral dryness- treatment

Salivary gland stimulation

Non-pharmacological

Gustatory stimulant

sugar free acidic candies

Lozenges

Xylitol

Mechanicals stimulants

Pharmacological

Oral muscarinic agonist : Pilocarpine, SALAGEN®

Magistral preparation for therapeutic use
capsules of HYDROCHLORIDE PILOCARPINE hydrochloride
capsules 4 mg: 3 to 4 capsules a day

Saliva substitutes

Sjögren syndrome
Treatment for systemic symptoms

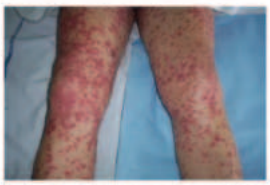
- Lack of robust evidence
  Only few Randomized clinical trial
- Extrapolation from others autoimmune diseases
  mainly empirical and symptom-targeted
- EULAR recommandations 2019

Cryoglobulinemia vasculitis
treatment

Proliferative glomerulonephritis : rare
Cryoglobulinemia related*

High activity :
First line : **GC** 0.5-1 mg/kg/day
Second line : **RTX*** if cryo vasculitis
or CYC
Rescue : CYC +/- PEX *if life treathening
cryo -vasculitis

RITUXIMAB 375 mg/m2 W1 W2 W3 W4
(not 1 gramme at D1 D15) Risk of serum disease
Risk of anti-rituximab immunisation

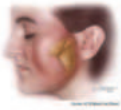


Cutaneaous vasculitis
High activity :
First line : **GC** 0.5-1 mg/kg/day
Second line : Oral **ID**
or **RTX** if cryo vasculitis
Rescue: **CyC**
+/- Plasma exchange (PEX) if life treathening
cryo -vasculitis

Treatment for systemic symptoms

Glucocorticosteroids (GS)

Active systemic disease ESSDAI
Minimum dose
Shortest time



PAROTIDIS AND GLANDULAR INVOLVEMENT

First line
Symptomatic, massage

Second line : glucocorticosteroids (**GC**) **0.3 mg/kg/d**

SYNOVITIS

First line
NSAID 7days max + HCQ 200mg/day

Moderate to high : Oral **GC 0,3mg/kg/d**
short term course

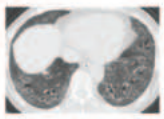
Seror R et al. ESSDAI. RMD open 2015

Ramos-Casals M *et al.* Ann Rheum Dis 2020. EULAR recommendations

Treatment for systemic symptoms

Glucocorticosteroids (GS)

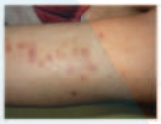
Active systemic disease ESSDAI
Minimum dose
Shortest time



INTERSTITIAL LUNG DISEASE
Moderate 1rst Line : **GC 0,5 mg**/kg/d
LIP and OP,
less in NSIP
and even less in UP

High : **1rst Line** : **GC 0,5-1 mg**/kg/d

TUBULO INTERSTITIAL NEPHROPATHY
Moderate 1rst Line : **GC 0,5 mg**/kg/d



CUTANEOUS VASCULITIS
Moderate : GC 0,3 mg/kg/

Seror R et al. ESSDAI. RMD open 2015

Ramos-Casals M *et al.* Ann Rheum Dis 2020. EULAR recommendations

Treatment for systemic symptoms

Hydroxychloroquine (HCQ)

Retrospective study
Open label study

Randomized Clinical Trial (RCT)
no effect

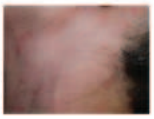
Leflunomide + HCQ RCT =1

ARTHRALGIA
First line : NSAID
Second line : Hydroxychloroquine **HCQ**
expert advice
No RCT

SYNOVITIS
First line
NSAID 7days max + **HCQ 200mg/day**

ANNULAR ERYTHEMA

Limited : Topical GC



Diffuse :
1rst line : **HCQ** and/or GC 0,3 mg/kg/day
Second line: other antimalarial +/- GC 0.5-1 mg/kg/day

Seror R et al. ESSDAI. RMD open 2015
Ramos-Casals M *et al.* Ann Rheum Dis 2020. EULAR recommendations

Leflunomide–hydroxychloroquine combination therapy in patients with primary Sjögren's syndrome (RepurpSS-I): a placebo-controlled, double-blinded, randomised clinical trial

From 0 to 24 weeks, the mean difference in ESSDAI score, adjusted for baseline values, in the leflunomide-hydroxychloroquine group compared with the placebo group was -4·35 points (95% CI -7·45 to -1·25, p=0·0078).

van der Heijden EH *et al.* Lancet Rheumatol 2020

Sjögren
Treatment for systemic symptoms

Immunosuppressive drug (ID)

Methotrexate
Azathioprine
Mycophenolate mofetil
Cyclophophamide

No RCT
2nd line

SYNOVITIS
Second line : immunosuppressive drug (ID)

INTERSTITIAL LUNG DISEASE
High : 2nd Line : ID

TUBULO INTERSTITIAL NEPHROPATHY
Moderate 2nd Line :Oral ID
(azathioprine, ciclosprine, MMF)

Sjögren
Treatment for systemic symptoms

RITUXIMAB (RTX)

RCT n=4
systemic disease not endpoint

Reference	Endpoint	Population n=	results
Bowman 2017 Arthritis Rheumatol. 2017	Fatigue Oral Dryness	133 Placebo n=66 Rituximab 67	Fatigue :No efficiciency Unstimulated salivary flow +/_
Dass 2008	Fatigue	17 Placebo Rituximab	Efficiency
Devauchelle-Pensec V et al Ann Intern Med 2014	Fatigue Pain Dryness	120 Placebo n= 60 Rituximab n =60	No efficiency
Meijer JM et al. Arthritis Rheum 2010	Salivary flow	30 Placebo n=10 Rituximab n	efficiency

Sjögren
Treatment for systemic symptoms

TABLE 4 Recommendations for the off-label biological therapy in Sjögren's syndrome.

Recommendation (clinical circumstance and drug)	LoE a)	GoR a)	Off-label guidance b)
First-line therapy			
1. In pts with SS and with sicca symptoms only, biological therapy is not recommended.	1a	A	IV
2. In pts with SS and severe systemic manifestation, with risk of lymphoma (at least 3 risk factors for lymphoma) and recent onset (<12 months of evolution), RTX can be used as first-line therapy.	4	C	II
3. RTX may be used as first-line therapy in pts with SS (<12 months of evolution) and peripheral neuropathy, severe thrombocytopenia, severe CNS disease, severe parotid swelling, and/or cryoglobulinemic vasculitis.	1b	B	II
4. RTX may be used as first-line therapy in pts with SS (>12 months of evolution) and peripheral neuropathy, severe thrombocytopenia, severe CNS disease, severe parotid swelling, and/or cryoglobulinemic vasculitis.	2b	C	II
5. Fatigue in SS patients is not a recommendation for biological therapy.	1a	A	IV
Second-line therapy			
6. RTX is recommended in pts with refractory SS who present the systemic manifestations indicated for the first-line therapy.	1b	B	I
7. In RTX-experienced pts, sequential therapy of BEL-RTX may be used.	2b	C	II

Levels of evidence and strength of recommendations

Levels	Type of evidence	Strength	Evidence-based
1a	Systematic review of RCTs	A	Consistent level 1 studies
1b	Individual RCT		
2a	Systematic review of cohort studies	B	Consistent level 2 or 3 studies
2b	Individual cohort study		Extrapolations from level 1 studies
2c	Outcomes research / ecological studies		
3a	Systematic review of case-control studies		
3b	Individual case-control study		
4	Case-series / retrospective studies / low-quality cohort or case-control studies*	C	Consistent level 4 studies
5	Expert opinion	D	Consistent level 5 evidence

* low quality defined according to the Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009)

TABLE 1 Guidance for off-label use of biological therapy.

	Categories	Availability
I	Recommended use	Often used in clinical practice for other autoimmune diseases
II	Suggested use	Used in patients with specific characteristics or underlying clinical conditions
III	Possible use	Not contraindicated and successful case reports/series available
IV	Use not recommended	No additional benefit
V	Use not recommended	Contraindicated use

Marinho A *et al.* Front Immunol 2023

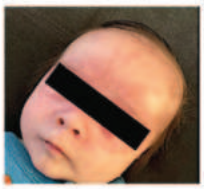
Pregnancy

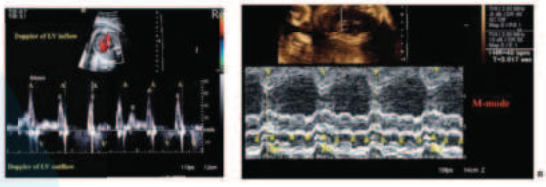
Anti-SSA ab and neonatal lupus : 0.7-2%
- skin
- hematologic
- liver

Transitory symptom

- **heart**

Congenital atrioventricular heart block cAVHB
Mortality 10% in utero. 10 % post-natal
permanent
Recurrency 17-19%





From 16 to 24-26 week of gestation
monitoring ultrasound every 2week ?

Or lightest monitoring : only + 1 ultrasound at 26 WG

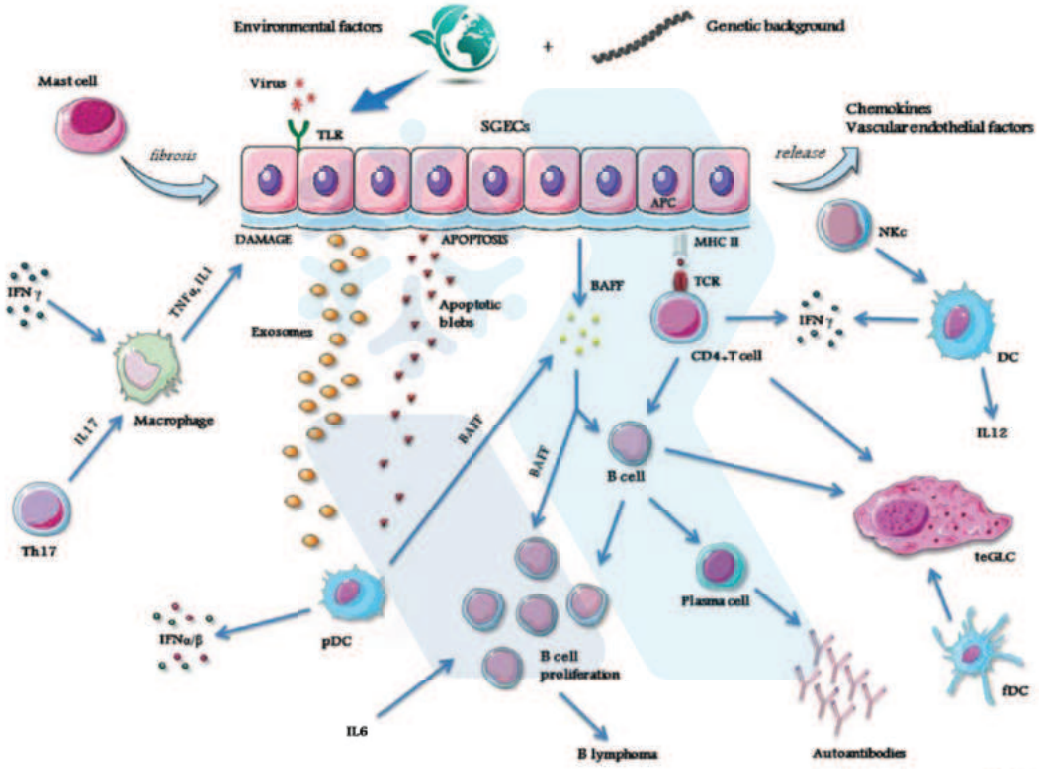
99% : normal
If cAVHB No treatment
Fluoro Glucocorticoids : no validated

Delivery near a specialized pediatric cardiology setting

Previous cAVHB
Hydroxychloroquine HCQ 400mg/d
given no later than 8weeks of gestation
a decreased risk 50%

Monitoring from 16 to 28 gestational week
every week

Devauchelle-Pensec *et al.* Rev Med Int 2023

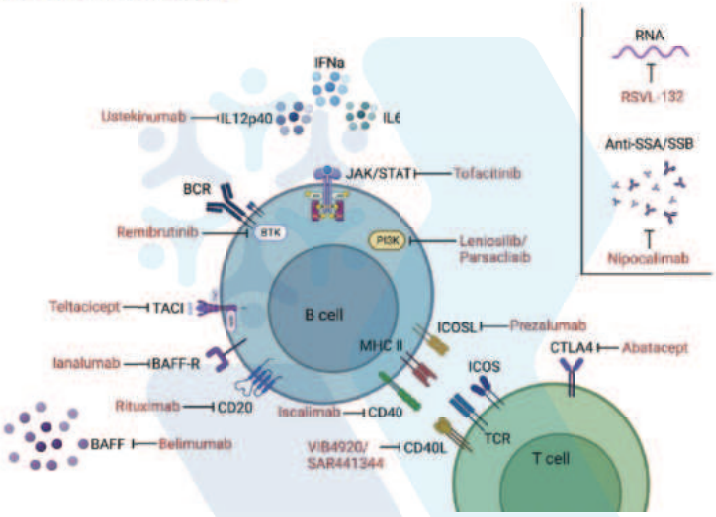


Vitali C *et al*. Frontiers in Medicine 2021

Clinical trials Since EULAR recommandation : New therapeutics strategy

Primary outcome of improvement in ESSDAI score in randomized placebo-controlled trials RCT

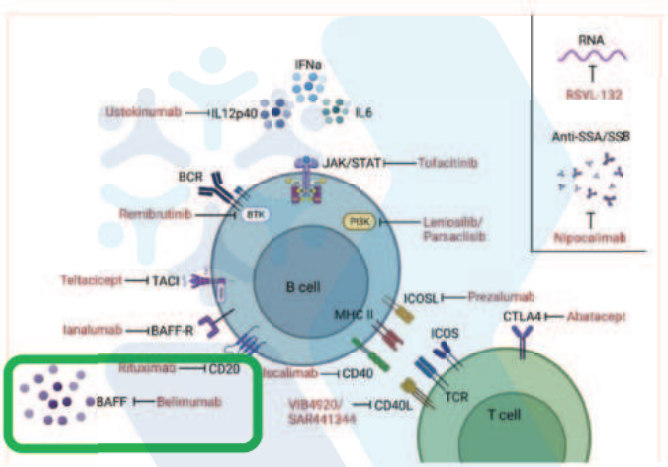
BLOCKING THE B LYMPHOCYTE PATHWAY

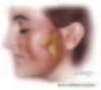


Ritter *et al*. Joint Bone Spine 2022

> Anti-BAFF : Belimumab
> Anti BAFF et ANTI CD20 : Sequential belimumab and rituximab

ESSDAI



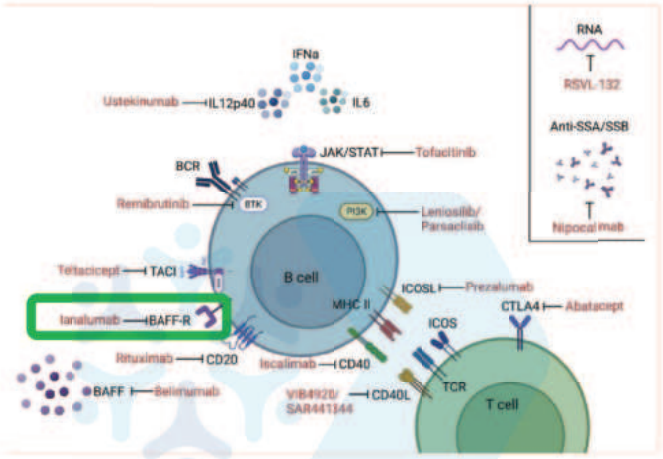


Efficacy and safety of belimumab given for 12 months in primary Sjögren's syndrome: the BELISS open-label phase II study
De Vita S *et al.* Rheumatology 2015

A randomized, phase II study of sequential belimumab and rituximab in primary Sjögren's syndrome
Mariette X *et al.* JCI Insight 2022

>Block BAFF Receptor : Ianalumab

ESSDAI
Saliva flow

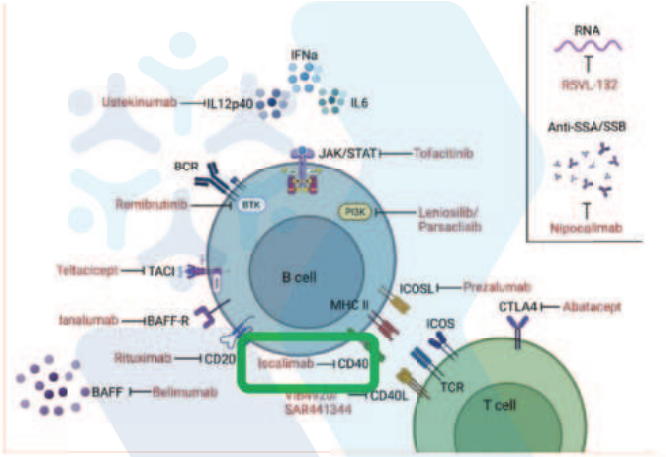


Safety and efficacy of subcutaneous ianalumab (VAY736) in patients with primary Sjögren's syndrome: a randomised, double-blind, placebo-controlled, phase 2b dose-finding trial
Bowman SJ *et al.* Lancet 2022

52-Week Results From a Randomized, Placebo-Controlled, Phase 2b Dose-Ranging Study
Dörner T *et al.* Arthritis Rheum 2024

> INHIBIT B CELL ACTIVATION CD40/CD40L pathway
Iscalimab (anti-CD40 monoclonal antibody)

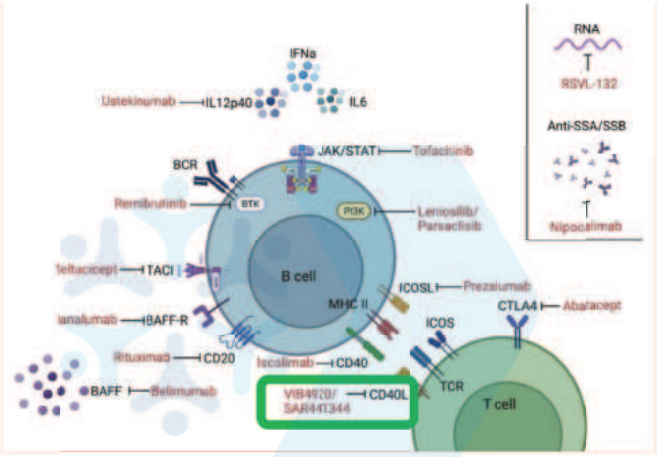
ESSDAI



Safety and efficacy of subcutaneous iscalimab (CFZ533) in two distinct populations of patients with Sjögren's disease (TWINSS): week 24 results of a randomised, double-blind, placebo-controlled, phase 2b dose-ranging study
Fisher B *et al*. Lancet 2024

> INHIBIT B CELL ACTIVATION CD40/CD40L pathway
dazodalibep CD40 ligand antagonist

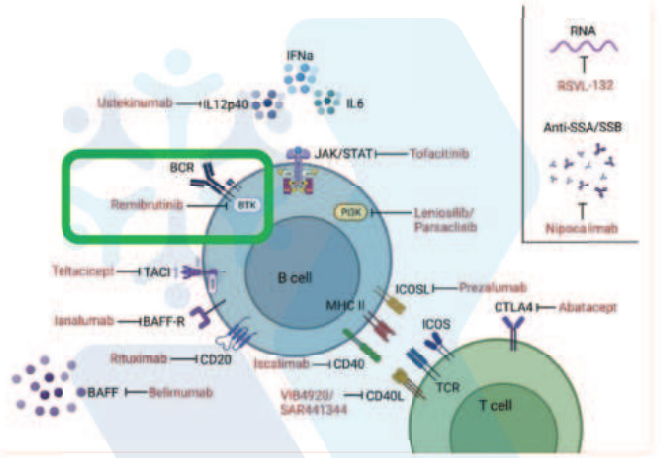
ESSDAI
Constitutional
Lymphadenopathy



CD40 ligand antagonist dazodalibep in Sjögren's disease: a randomized, double-blinded, placebo-controlled, phase 2 trial
St Clair EW *et al*. Nat Med 2024

> INHIBIT INTRA CELLULAR SIGNALING
BTK Inhibitor Remibrutinib

ESSDAI
Saliva flow



Efficacy and safety of remibrutinib, a selective potent oral BTK inhibitor, in Sjögren's syndrome: results from a randomised, double-blind, placebo-controlled phase 2 trial

Dörner T *et al.* Ann Rheum Dis 2024

Conclusion

70% : **begnin course**
BUT
poor quality of life
fatigue, pain, disabling dryness

30% : **systemic disease** , sometimes severe disease

5% : Lymphoma

Treatment :
Guidelines cryoglobulinemic vasculitis

For other symptoms :**expert opinion EULAR 2019**

Now and In future :
Randomized Clinical Trial
Endpoint ESSDAI ESSPRI

Main target : B lymphocyte activation pathway


CÁM ƠN MERCI THANK YOU