APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA
5ª edizione
REUMATOLOGIA E MALATTIE NEOPLASTICHE

Sjögren's: a lymphoproliferative syndrome

Torino, 13-14 ottobre 2017

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Sjögren's syndrome

SS is an **autoimmune and lymphoproliferative syndrome** mainly characterized by:

-sicca symptoms (90-95% of pts) due to an inflammatory lymphocytic glandular infiltration and destruction, but also by

- a wide range of possible systemic manifestations (occurring in about 30-40% of pts).

•SS hallmark: **B cell hyperactivity**

- overproduction of autoantibodies, (anti-Ro/SSA, anti-La/SSB, rheumatoid factor (RF), cryoglobulins)

- significant expansion of B cell clonal populations → possible evolution to NHL

The ACR/EULAR Classification Criteria for Primary Sjoegren's Syndrome

Item	Weight/score
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥ 1 foci/4mm^2	3
Anti-SS-A/Ro positive	3
Ocular Staining Score ≥ 5 (or van Bijsterveld score ≥ 4) in at least one eye	1
Schirmer's test ≤ 5 mm/5 minutes in at least one eye	1
Unstimulated whole saliva flow rate ≤ 0.1 ml/minute	1

A score ≥ 4 classifies a patient who meets the **inclusion criteria:**

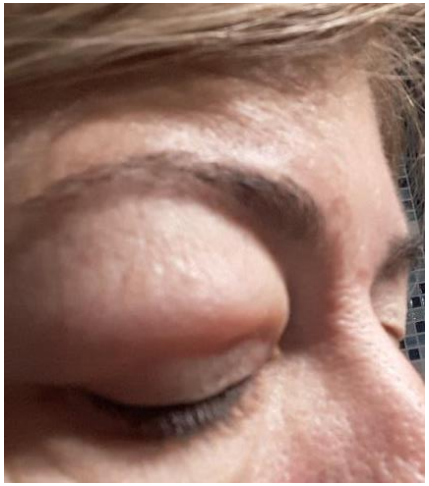
- ocular and/or oral dryness or suspicion of SjS according to EULAR SjS Disease Activity Index (ESSDAI)

and does not have any of the **exclusion criteria:**

- history of head and neck radiation, active HCV infection, AIDS, sarcoidosis, amyloidosis, graft-versus-host disease, IgG4-related disease.

Sjögren's syndrome associated lymphoma

•About 5% of SS pts develop a **B cell NHL**, with a higher risk, ranging from 6.1- to 44.4-fold, compared to general population.

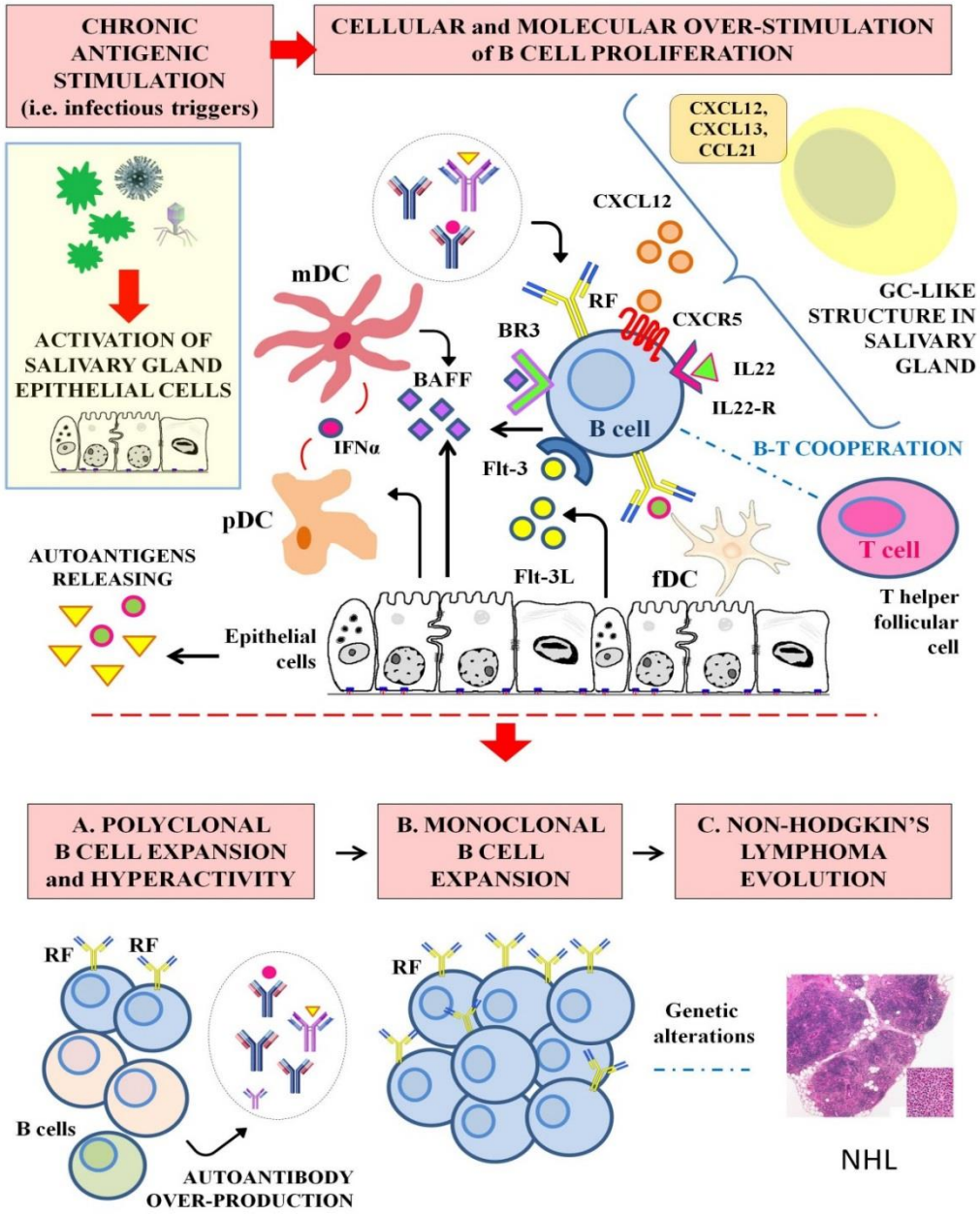


-Late complication (7.5 yrs after SS diagnosis)
- Median age at diagnosis of NHL: 58 yrs.
-No gender predisposition
-Sites of involvement include minor and/or major salivary glands, lacrymal glands, stomach, lungs, nodes, breast...
-Involvement of bone marrow is rare.

• **Subtypes**

-Marginal zone B cell lymphoma (MZBCL) of the **MALT** (Mucosa associated Lymphoid Tissue) **type**
-Nodal MZBCL
-Diffuse Large B cell Lymphoma (DLBCL)

• **Lymphoma** represents the main cause of **mortality** in SS pts.



Gandolfo S, 2015

Research efforts:

- **To identify biomarkers**
- **To stratify patients**

HORIZON-2020

HARMONIzation and integrative analysis of regional, national and international Cohorts on primary Sjögren's Syndrome (pSS) towards improved stratification, treatment and health policy making

- Harmonize the definitions and procedures
- Define and validate biomarkers
- Integrate biomarkers
- **Stratify patients**
- Define outcomes
- Design clinical trials
- **Give to the patients an effective therapeutic chance**

Recommendation

Standardisation of labial salivary gland histopathology in clinical trials in primary Sjögren's syndrome

Benjamin A Fisher,[1,2] Roland Jonsson,[3,4] Troy Daniels,[5] Michele Bombardieri,[6] Rachel M Brown,[7] Peter Morgan,[8] Stefano Bombardieri,[9] Wan-Fai Ng,[10] Athanasios G Tzioufas,[11] Claudio Vitali,[12] Pepe Shirlaw,[13] Erlin Haacke,[14] Sebastian Costa,[15] Hendrika Bootsma,[16] Valerie Devauchelle-Pensec,[17] Timothy R Radstake,[18] Xavier Mariette,[19] Andrea Richards,[20] Rebecca Stack,[1] Simon J Bowman,[1,2] Francesca Barone,[1] on behalf of the Sjögren's histopathology workshop group (appendix) from ESSENTIAL (EULAR Sjögren's syndrome study group)

History of research about adverse predictors in SS (1)

Ann Intern Med. 1978;89(6):888-892.

Increased Risk of Lymphoma in Sicca Syndrome

STUART S. KASSAN, M.D.; TERRY L. THOMAS, M.S.; HARALAMPOS M. MOUTSOPOULOS, M.D.; ROBERT HOOVER, M.D.; ROBERT P. KIMBERLY, M.D.; DANIEL R. BUDMAN, M.D.; JOSE COSTA, M.D.; JOHN L. DECKER, M.D.; and THOMAS M. CHUSED, M.D.

Persistent **parotid enlargement, lymphadenopathy and/or splenomegaly** important clinical signs for lymphoma development (Kassan et al., 1978)

ARTHRITIS & RHEUMATISM
Vol. 39, No. 5, May 1996, pp 767–772

MIXED MONOCLONAL CRYOGLOBULINEMIA AND MONOCLONAL RHEUMATOID FACTOR CROSS-REACTIVE IDIOTYPES AS PREDICTIVE FACTORS FOR THE DEVELOPMENT OF LYMPHOMA IN PRIMARY SJÖGREN'S SYNDROME

ATHANASIOS G. TZIOUFAS, DIMITRA S. BOUMBA, FOTINI N. SKOPOULI, and HARALAMPOS M. MOUTSOPOULOS

First demonstration of association between **cryoglobulinemia** and the risk of lymphoma (Tzioufas et al., 1996)

History of research about adverse predictors in SS (2)

• **Low C4** as the strongest predictor for mortality in SS (Skoupoli et al., 2000).

• **Parotid enlargement, purpura and low C4** as independent lymphoma risk factors in SS (Ioannidis et al., 2002)

Two category of different risk on the basis of purpura and/or low C4 presence or absence respectively:

-type I-high risk: 20% of pts

-type II-low risk: 80% of pts

• **Parotid swelling, cryo, purpura and low C4**: if 2/4 of these factors are present SS pts have a decreased survival (Brito-Zeron et al., 2007).

History of research about adverse predictors in SS (3)

ARTHRITIS & RHEUMATISM
Vol. 50, No. 4, April 2004, pp 1262–1269

Mortality and Causes of Death in Primary Sjögren's Syndrome

Elke Theander, Rolf Manthorpe, and Lennart T. H. Jacobsson

- **Hypocomplementaemia** associated with the main adverse outcome scenarios in SS pts: lymphoma and death (Theander et al., 2004; Ramos-Casals et al., 2005; Solans-Laquè et al., 2011).

- **Neutropenia, low C4, cryo, lymphadenopathy, splenomegaly** independent predictors for MALT lymphoma development (Baimpa et al., 2009)

- **Lymphocytopenia $CD4^+$ and a $CD4^+/CD8^+$ ratio ≤0.8**: risk factors for lymphoma (Theander et al., 2006)

Histopathology of salivary glands

- **GC-like structures detection** (Theander et al., 2011)
- **Lymphocytic Focus Score ≥3** (Risselada et al., 2014)

In both cases: significant association with lymphoma development.

Ann Rheum Dis 2011;**70**:1363–1368.

Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjögren's syndrome

Elke Theander,[1] Lilian Vasaitis,[2] Eva Baecklund,[2] Gunnel Nordmark,[2] Gunnar Warfvinge,[3] Rolf Liedholm,[4] Karl Brokstad,[5] Roland Jonsson,[5,6] Malin V Jonsson[5,7]

Conclusions The detection of GC-like structures by light microscopy in pSS diagnostic salivary biopsies is proposed as a highly predictive and easy-to-obtain marker for NHL development. This allows for risk stratification of patients and the possibility to initiate preventive B-cell-directed therapy.

Ann Rheum Dis 2014;**73**:1537–1540.

The prognostic value of routinely performed minor salivary gland assessments in primary Sjögren's syndrome

Anna P Risselada,[1] Aike A Kruize,[1] Roel Goldschmeding,[2] Floris P J G Lafeber,[1] Johannes W J Bijlsma,[1] Joel A G van Roon[1]

Conclusions Routine histopathological minor salivary gland assessment has important prognostic value. The LFS might help to identify patients with an increased risk for lymphoma.

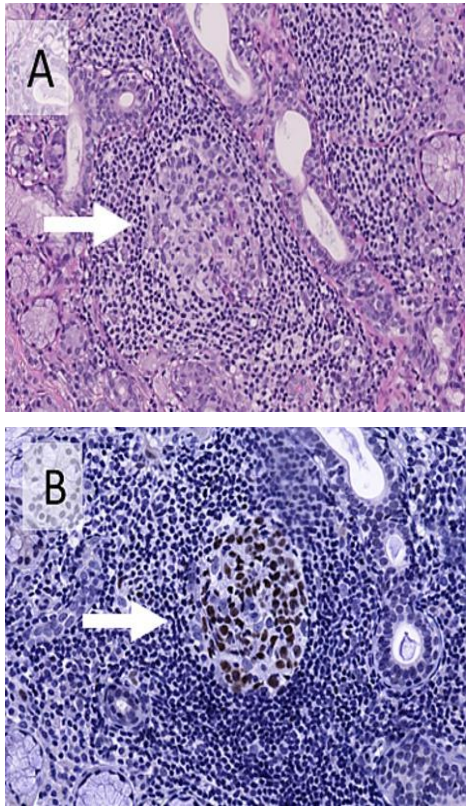
GCs in pSS

- Ectopic Germinal centre (GC)-like structures have been identified in pSS SG (Amft N, 2011; Pitzalis C, 2014).

- GCs in pSS express the AID responsible for SHM and CSR, also in pSS with lymphoma (Bombardieri M, 2007), owning a complete machinery for B cells clonal expansion.

- Autoreactive B cells persist in GCs in pSS and by-pass traditional checkpoints controls (Le Pottier L, 2009).

- **Different ways to evaluate ectopic GCs** (triple-staining, double staining, sequential sections-staining), **different definitions.**

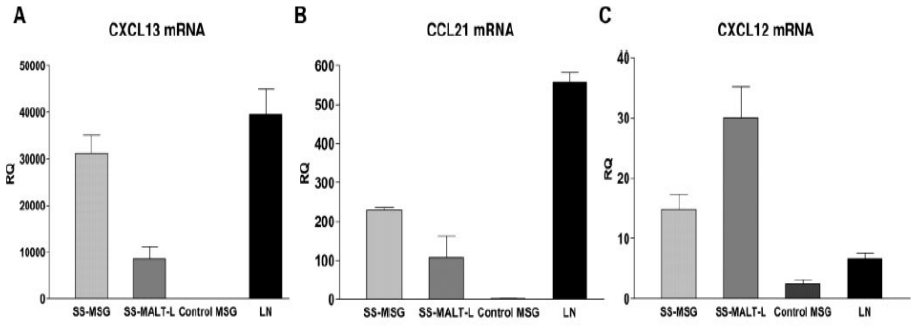


Haacke E A, 2017

New biomarkers: Chemokines

CXCL13, CCL21, and CXCL12 Expression in Salivary Glands of Patients with Sjögren's Syndrome and MALT Lymphoma: Association with Reactive and Malignant Areas of Lymphoid Organization[1]

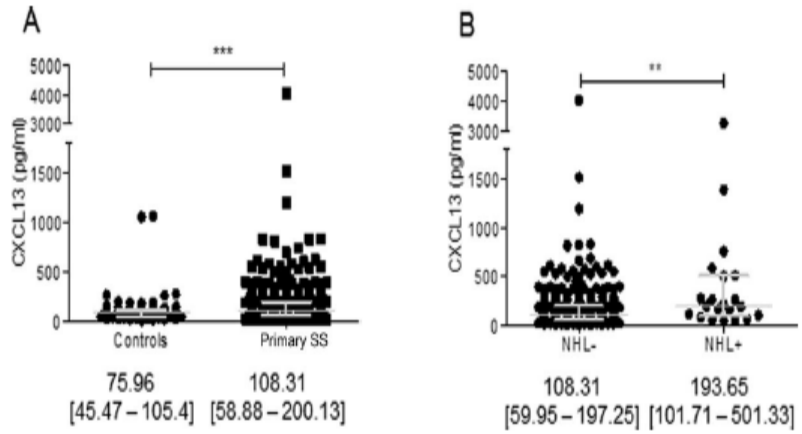
J Immunol 2008; 180:5130-5140



ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 12, December 2015, pp 3226–3233
DOI 10.1002/art.39315

CXCL13 and CCL11 Serum Levels and Lymphoma and Disease Activity in Primary Sjögren's Syndrome

G. Nocturne,[1] R. Seror,[2] O. Fogel,[1] R. Belkhir,[3] S. Boudaoud,[1] A. Saraux,[4] C. Larroche,[5] V. Le Guern,[6] J. E. Gottenberg,[7] and X. Mariette[2]



Polymorphisms of the CXCR5 gene that codify for the receptor of CXCL12 have been associated both with pSS and SS-unrelated NHL (Song R, 2012)

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

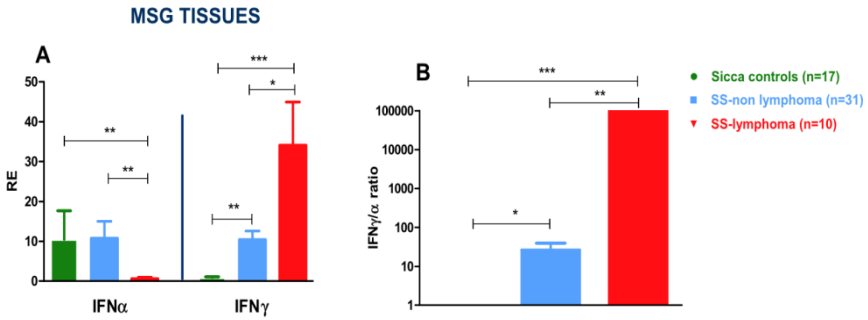
New biomarkers: IFN signature

Type I and II interferon signatures in Sjogren's syndrome pathogenesis: Contributions in distinct clinical phenotypes and Sjogren's related lymphomagenesis

Adrianos Nezos [a], Fotini Gravani [b], Anna Tassidou [c], Efstathia K. Kapsogeorgou [d], Michael Voulgarelis [d], Michael Koutsilieris [a], Mary K. Crow [e, 1], Clio P. Mavragani [a, d, 1, *]

Contribution of both type I and II IFN signatures in distinct clinical phenotypes of SS:

- Peripheral IFN type I : SG swelling, SSA, lymphopenia
- Peripheral I and II: hypergamma
- MSG IFN I: arthralgias
- MSG IFN II: purpura, low C4



Highlights

- Type I IFN signature predominates in the peripheral blood of primary SS patients.
- Type II IFN signature prevails in minor salivary gland tissues of primary SS patients.
- IFNγ/α mRNA ratio in MSG biopsies can serve as a biomarker of prediction of in situ SS-related lymphoma.
- Type I and II IFN signatures were related to distinct SS clinical/serological phenotypes.

Terapia anti-IFN?
Quale?

Adverse predictors summary

CLINICAL FEATURES

Persistent glandular swelling

Purpura

Lymphoadenomegaly

Splenomegaly

LABORATORY FINDINGS

Cryoglobulinaemia

Low C4 levels

Low C3 levels

Leukopenia (lympocytopenia T CD4)

Anti-Ro/SSA , Anti-La/SSB

HYSTOPATHOLOGY OF SALIVARY GLANDS

GC-like structures detection - MALT acquisition

Local Monoclonal B cell Expansion

Lymphocytic Focus Score ≥3

NOVEL BIOMARKERS

Persistent glandular swelling

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journal homepage: www.elsevier.com/locate/jautimm

SG swelling : 30% of SS pts
NHL: 5-10% of SS pts

Which pts with SG swelling should be considered at higher risk of NHL development?

Biomarkers of lymphoma in Sjögren's syndrome and evaluation of the lymphoma risk in prelymphomatous conditions: Results of a multicenter study

Luca Quartuccio [a], Miriam Isola [b], Chiara Baldini [c], Roberta Priori [d], Elena Bartoloni Bocci [e], Francesco Carubbi [f], Marta Maset [a], Giorgia Gregoraci [b], Vincenzo Della Mea [g], Sara Salvin [a], Ginevra De Marchi [a], Nicoletta Luciano [c], Serena Colafrancesco [d], Alessia Alunno [e], Roberto Giacomelli [f], Roberto Gerli [e], Guido Valesini [d], Stefano Bombardieri [c], Salvatore De Vita [a,*]

661 pSS pts, HCV neg, classified according to AECG criteria

4 groups:
- Group 1: pts CV+ and/or salivary glands swelling+, lymphoma +
- Group 2: pts CV+, lymphoma –
- Group 3: pts salivary glands swelling +, lymphoma –
- Group 4: pts CV-, salivary glands swelling-, lymphoma -

Results

• The study shows that 4 biomarkers, cryo, low C4, anti-SSB, leukopenia were significantly associated to lymphoma.

Multivariate analyses.

	Group 1/NHL ($n = 40$), RRR (95% CI)	Group 2/CV ($n = 17$), RRR (95% CI)	Group 3/SW ($n = 180$), RRR (95% CI)	Group 4/pSS controls ($n = 424$)
Anti-SSB/La	5.2** (2.3–11.9)	1.5 (0.3–6.5)	1.3 (0.9–1.9)	Reference group
Leukopenia (<3000/mmc)	3.3* (1.5–7)	2.6 (0.6–11.4)	0.9 (0.6–1.4)	Reference group
Low C4	8.3** (3.6–19.2)	3.8 (0.9–16.3)	1.5 (0.9–2.7)	Reference group
Serum cryoglobulins	6.8* (2.1–22.3)	NA	1.3 (0.4–4.3)	Reference group

RRR, related risk ratio; CI, confidence interval; and NA, not applicable, because of 100% patients positive for serum cryoglobulins in the CV group.
*$P < 0.005$; and **$P < 0.0001$.

• In the presence of salivary glands swelling without lymphoma **if 2/4** of these biomarkers **are positive** → 9-fold risk of lymphoma.

Cryoglobulinaemia and cryoglobulinaemic vasculitis (CV) - 1

CV is frequently a complication of **HCV infection** (80-90% of cases of CV). Among HCV-neg cases, **SS** is the largest subgroup of CV pts. **Both HCV infection and SS predispose to B-cell NHL**.

Satisfied if at least two of the three items (questionnaire, clinical, laboratory) are positive
the patient must be positive for serum cryos in at least 2 determinations at ≥ 12 week interval

(i) **Questionnaire item**: at least two out of the following	
• Do you remember one or more episodes of small red spots on your skin, particularly involving the lower limbs?	
• Have you ever had red spots on your lower extremities which leave a brownish color after their disappearance?	
• Has a doctor ever told you that you have viral hepatitis?	
(ii) **Clinical item** : at least three out of the following four (present or past)*	
• Constitutional symptoms	Fatigue Low grade fever (37–37.9°C, >10 days, no cause) Fever (>38°C, no cause) Fibromyalgia
• Articular involvement	Arthralgias Arthritis
• Vascular involvement	Purpura Skin ulcers Necrotising vasculitis Hyperviscosity syndrome Raynaud's phenomenon
• Neurologic involvement	Peripheral neuropathy Cranial nerve involvement Vasculitic CNS involvement
iii. **Laboratory item** : at least two out of the following three (present)	
• Reduced serum C4	
• Positive serum rheumatoid factor	
• Positive serum M component	

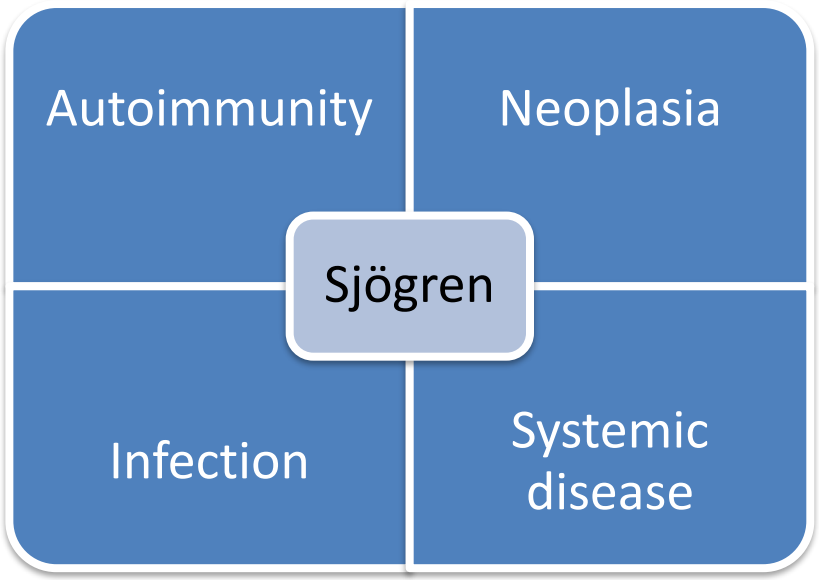
Preliminary classification criteria for the cryoglobulinaemic vasculitis

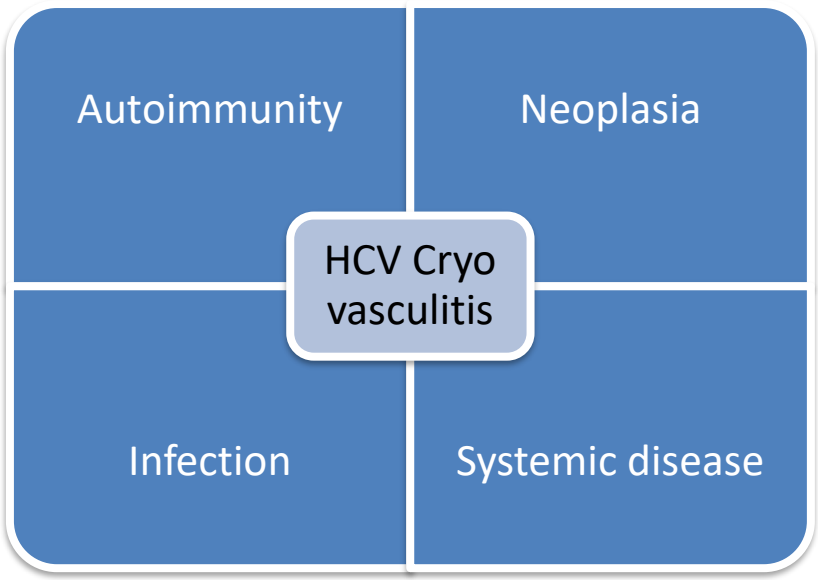
De Vita et al., 2011

Validation of the classification criteria for cryoglobulinaemic vasculitis

Quartuccio et al., 2014

The complex world of Sjögren's syndrome and CV





Cryoglobulinemia in Sjögren Syndrome: A Disease Subset that Links Higher Systemic Disease Activity, Autoimmunity, and Local B Cell Proliferation in Mucosa-associated Lymphoid Tissue

Cryoglobulinaemia and cryoglobulinaemic vasculitis (CV) - 2

Performance of the preliminary classification criteria for cryoglobulinaemic vasculitis and clinical manifestations in hepatitis C virus-unrelated cryoglobulinaemic vasculitis

L. Quartuccio, M. Isola, L. Corazza, M. Maset, G. Monti, A. Gabrielli, A. Tzioufas, C. Ferri, G. Ferraccioli, M. Ramos-Casals, M. Voulgarelis, M. Lenzi, M. Mascia, D. Sansonno, P. Cacoub, M. Tomsic, A. Tavoni, M. Pietrogrande, A. Zignego, S. Scarpato, P. Pioltelli, S. Steinfeld, P. Lamprecht, M. Galli, S. Bombardieri, S. De Vita

- Sensitivity and specificity of the classification criteria for the CV were high in the group of SS pts.

- Comparing the subgroup of SS pts with CV (SS-CV) to the SS pts with only cryo+ without vasculitis (CwV):

  - no differences between the groups in clinical features of lymphoproliferation (lymphadenopathy, splenomegaly, salivary glands swelling, B symptoms).

  -malignant lymphoma was more frequent in CV group.

Purpura

In SS the clinical finding of purpura may be linked to the presence of cryo or to the hypergammaglobulinaemia.

Scand J Rheumatol 2015;44:36–41

Clinical and biological differences between cryoglobulinaemic and hypergammaglobulinaemic purpura in primary Sjögren's syndrome: results of a large multicentre study

652 SS pts

L Quartuccio[1], M Isola[2], C Baldini[3], R Priori[4], E Bartoloni[5], F Carubbi[6], G Gregoraci[2,7], S Gandolfo[1], S Salvin[1], N Luciano[3], A Minniti[4], A Alunno[5], R Giacomelli[6], R Gerli[5], G Valesini[4], S Bombardieri[3], S De Vita[1]

Results

- CV purpura: association with peripheral neuropathy, low C4, anti-La/SSB.
- Hypergammaglobulinemic purpura: association with RF, anti-Ro/SSA.
- **Lymphoma is only associated with CV.**

Conclusion: hypergammaglobulinemic purpura is an epiphenomenon of a benign B-cell lymphoproliferation, conversely **CV is linked to a higher risk of lymphoma and can be considered a prelymphomatous condition**.

CLINICAL-PROGNOSTIC TURNING

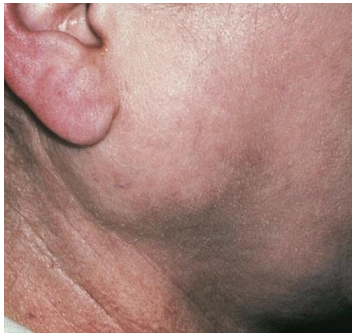
Heavy MALT acquisition of glands clinically leading to

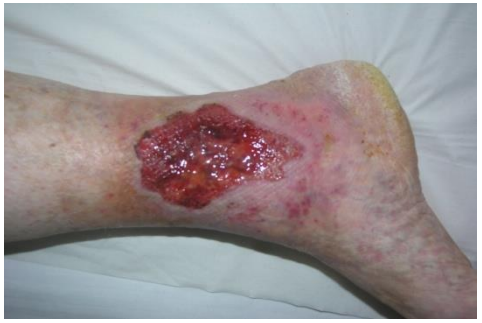
PERSISTENT GLANDULAR SWELLING

and

CRYOGLOBULINEMIA/CV

Biopsy





are the two main predictors of lymphoma and they can be considered as

Pre-lymphomatous conditions

Biologic treatment of Sjögren's syndrome

Biologics are currently the best potential option to treat SS.

Several clinical trials have tested biologic therapies efficacy and safety in SS using similar dose regimen to that in other autoimmune conditions: no homogeneous results, great heterogeneity among SS patients.

No drugs have been approved in SS.

- Therapies targeting classic pro-inflammatory cytokines (IL 1**, IL 6**, TNFα)
- Therapies targeting T cells and costimulation
- **Therapies targeting B cells**
- **Biologic therapies in SS-related lymphoma and combined/sequential therapy**
- Novel targets and ongoing trials

SS-related lymphoma and biologic therapies

Rituximab

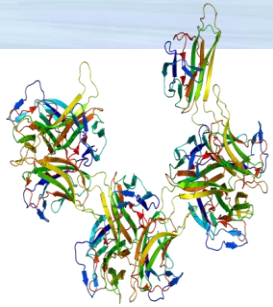
- **When cryoglobulinemia or cryoglobulinaemic vasculitis** (CV), that is a pre-lymphomatous condition, **is present**: rituximab is probably the best presently available treatment (De Vita S, 2012; Quartuccio L, 2013).
- RTX efficacy has been proved in SS pts with **severe systemic extraglandular** involvement and in those with **more active disease** (Gottenberg et al., 2013; Carubbi et al., 2013).
- **In the lack of cryo/CV**: rituximab use and efficacy is still **controversial** (Quartuccio L, 2009).

RTX might not deplete the B-cell infiltrate (De Vita S, 2002).

Heterogeneity of response possibly related to **local growth factors** influencing resistance/response to the anti-CD20 therapy.

- **Resistance to RTX** therapy related to local **BAFF over-expression** (Gong Q, 2005, Quartuccio L, 2008).

BAFF



BAFF (or B-Lys) is a member of the TNF family promoting B-cell activation and survival (Schneider P, 1999).

- Polymorphisms in the BAFF gene have been associated to both **NHL and SS** (Novak AJ, 2009; Nezos A, 2014).
- BAFF Receptor His159Tyr mutation prevalence increased in **pSS patients with NHL** (Papageorgiou A, 2015).
- BAFF transgenic mice display a **hyperactivity of B-cells** leading to a tissue and blood **lymphoid proliferation** in a picture resembling SS and SLE (Mackay F, 1999; Batten M, 2004) and resulting in **marginal zone NHL** after many years.
- **High levels of BAFF** are found in saliva, sera and in affected tissues of **SS patients** (Groom J, 2002; Mariette X, 2003; Daridon C, 2007).
- Higher levels are found in SS patients with **lymphoma or pre-lymphomatous conditions**, such as myoepithelial sialadenitis (MESA) and cryoglobulinaemic vasculitis (CV) (Quartuccio L, 2013).

EXTENDED REPORT

Efficacy and safety of belimumab in primary Sjögren's syndrome: results of the BELISS open-label phase II study

Xavier Mariette,[1] Raphaèle Seror,[1] Luca Quartuccio,[2] Gabriel Baron,[3] Sara Salvin,[2] Martina Fabris,[2,4] Frederic Desmoulins,[1] Gaétane Nocturne,[1] Philippe Ravaud,[3] Salvatore De Vita[2]

Ann Rheum Dis. 2015 Mar;74:526-31.

- Open label, phase II.
- Patients n° 31
- Belimumab dosage was: 10 mg/kg at w 0, 2 and then every 4 weeks to week 24.

•Primary endpoint evaluated at W28 was improvement in two of the five following items:
- ≥30% reduction in VAS dryness
-≥30% reduction in VAS fatigue
- ≥30% reduction in VAS musculoskeletal pain
- ≥30% reduction in physician VAS systemic
-≥25% reduction in serum levels of any of the following B cell activation biomarkers (free light chains of immunoglobulin, β2-microglobulin, monoclonal component, cryoglobulin, IgG) or ≥25% increase in C4 level.

• Secondary end-points were change from baseline to W28 in the following items: each of the five items of the primary endpoint, Schirmer's test, unstimulated salivary flow, ESSDAI, ESSPRI, SF36 quality-of-life index.

Table 1 Baseline characteristics of patients

	All patients n=30
Age (years), mean (SD)	49.5 (16.5)
Female (%)	30 (100.0%)
Disease duration (years), mean (SD)	5.7 (5.6)
Whole unstimulated salivary flow (<0.1 mL/min)	23 (76.7%)
Schirmer's test ≤5 mm	25 (83.3%)
Focus score ≥1	25 (83.3%)
Baseline focus score, mean (SD)	1.6 (1.5)
Anti-SSA antibodies	29 (96.7%)*
Anti-SSB antibodies	22 (73.3%)
Presence of cryoglobulinaemia	3/29 (10.3%)
Presence of lymphoma†	2 (6.7%)
Current background medication	
Corticosteroids	5 (16.7%)
Hydroxychloroquine	8 (26.7%)
Methotrexate	3 (10%)
Previous treatments	
Hydroxychloroquine	11 (36.7%)
Methotrexate	2 (6.7%)
Azathioprine	1 (3.3%)
Anti-TNF (infliximab or etanercept)	1 (3.3%)
Rituximab	7 (23.3%)
Reason for inclusion	
Systemic complications	20 (71.4%)
Recent onset disease	10 (34.5%)
Increase in B cell biomarker values	22 (81.5%)
ESSDAI (0–123), mean (SD)	8.8 (7.4)
ESSPRI (0–10), mean (SD)	6.4 (1.1)
Dryness (0–10), mean (SD)	7.8 (1.8)
Pain (0–10), mean (SD)	4.6 (2.6)
Fatigue (0–10), mean (SD)	6.9 (1.8)

†In both cases, it was stable parotid low-grade stage IE lymphoma of MALT type; these patients were not treated with belimumab due to lymphoma, but due to active cutaneous vasculitis (one case), sicca symptoms and B cell hyperactivation (one case), according to the study protocol.

• Results **W28**
- the primary endpoint was achieved in 18 (60%).
- the mean ESSDAI and ESSPRI decrease.
- significant changes in B cell biomarker values
- salivary flow and Schirmer's test did not change.

Clinical and Experimental Rheumatology 22014; **32**: 490-494.

Sequential therapy with belimumab followed by rituximab in Sjögren's syndrome associated with B-cell lymphoproliferation and overexpression of BAFF: evidence for long-term efficacy

S. De Vita[1], L. Quartuccio[1], S. Salvin[1], L. Picco[1], C.A. Scott[2], M. Rupolo[3], M. Fabris[1,4]

1997, 41 y SS pts with sicca, SSA, SSB, FR, cryo II, HCV neg.
2002 parotid enlargement → **MESA+monoclonal B expansion**
2003 **CV**: purpura, neuropathy, cutaneous ulceration, persistent parotid swelling (**low-grade MALT B-NHL**) →
RTX 375 mg/m2/w for 4 w → inefficacy
cyclophosphamide 9 g,then azathioprine → inefficacy
2005, feb: parotidectomy→ ulceration reduction,
PE → ulceration resolution.
Persistence of the other clinical manifestations.
2005, sep: reactivation of leg ulceration → inefficacy of PE
2006 RTX 375 mg/m2/w for 8 w + high dose of steroids → inefficacy.
2006-2010: autograft, mycophenolate, prostacycline → inefficacy

2010 **belimumab** (trial BELISS) → worsening of ulceration after 5 infusions.

49 days after last BEL infusion: **RTX** 375 mg/m2/w for 4 w, retreatment at +6m and +12 m.

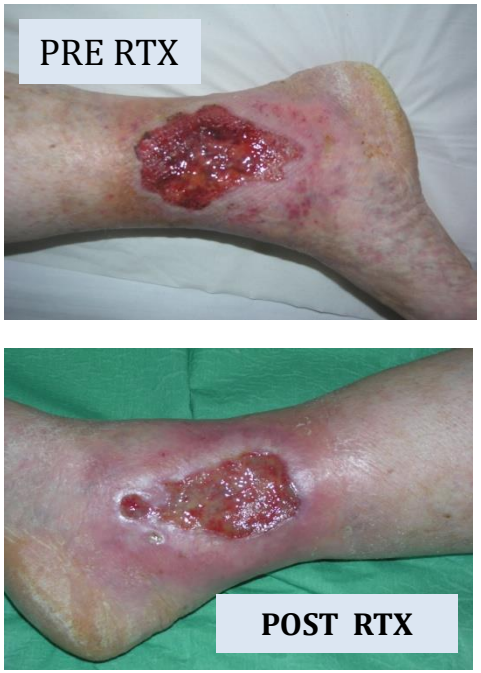


Table I. Summary of the clinical, laboratory and histologic features of the patient's history.

Therapy	2003 Nov RTX pre/post	2006 Mar RTX + high dose GCs pre/post	2010 Jun BEL pre/post	2010 Nov RTX pre/post	2011 July RTX pre/post	2012, Jan RTX pre/post	2013 Oct Last follow-up
Clinic							
Parotid swelling (ultrasound width*)	+/+ (25 mm/24 mm)	+/+	+/+	+/↓ (24 mm/18 mm)	↓/↓↓ (18 mm/13 mm)	↓↓/- (13 mm/7.5 mm)	- (7.5 mm)
Skin ulcer	+/+	+/+	+/+	+/↓	↓↓/↓	-/-	-/-
Peripheral neuropathy	+/+	+/+	+/+	+/+	+/+	+/+	+/+
Histology							
Parotid biopsy	Low grade MALT B-NHL				Sialadenitis focus score 1,648	Sialadenitis focus score 0,759	
Lip biopsy			Low grade MALT B-NHL	→			
Laboratory							
Cryoglobulins	+/+	+/+	+/-	+/-	-/-	-/-	-
RF (IU/l)	9190/23500	13400/866	638/413	413/109	95/77	72/-	-
Serum monoclonal component	IgM k/IgM k	IgM k/IgM k	IgM k/IgM k	IgM k/IgM k	IgM k/-	-/-	-
C4 (mg/dl)	7/7	5/5	0/1	1/6	8/15	19/25	31
BAFF (pg/ml)	2038/3866	3961/7726	13512/13064	14271/19580	2580/4194	2058/918	759
IgG (mg/dl)	3249/3412	2448/941	1529/1128	1128/895	851/838	862/787	811
IgA (mg/dl)	346/409	374/240	254/213	213/192			
IgM (mg/dl)	1351/1107	466/156	295/157	157/52			
Blood B-cells (CD19+)	7%/neg	5,5%/neg	33%/11%	11%/neg			
ANA titre	1:1280	1:1280	1:1280	1:1280			
Anti-SSA/SSB Abs	+/+	+/+	+/+	+/+			

RTX: Rituximab; GCs: Glucocorticoids; BEL: Belimumab; RF: Rheumatoid Factor; ↓: <25% decrease in s
from baseline; ↓↓: 25%–75% decrease in skin ulcer diameter or parotid gland enlargement from baseline.
*The width of the right parotid gland was measured in the transversal plane using a 6-18 MHz linear scanne

Progressive clinic resolution

Regression of lymphoma

Improvement of laboratory parameters

Sequential therapy BEL+RTX:
1 published case

Combined therapy BEL+RTX:
Ongoing clinical Trial
(NCT 02631538)

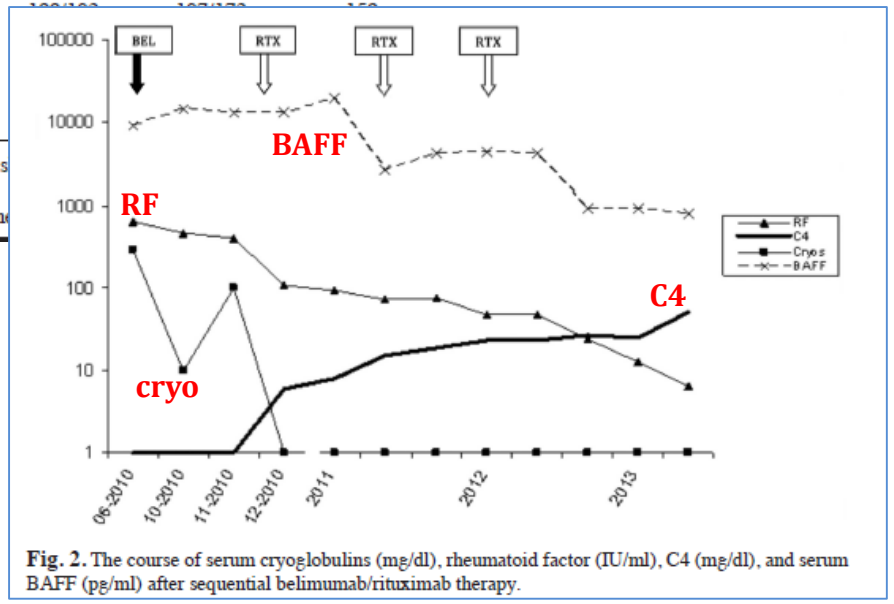
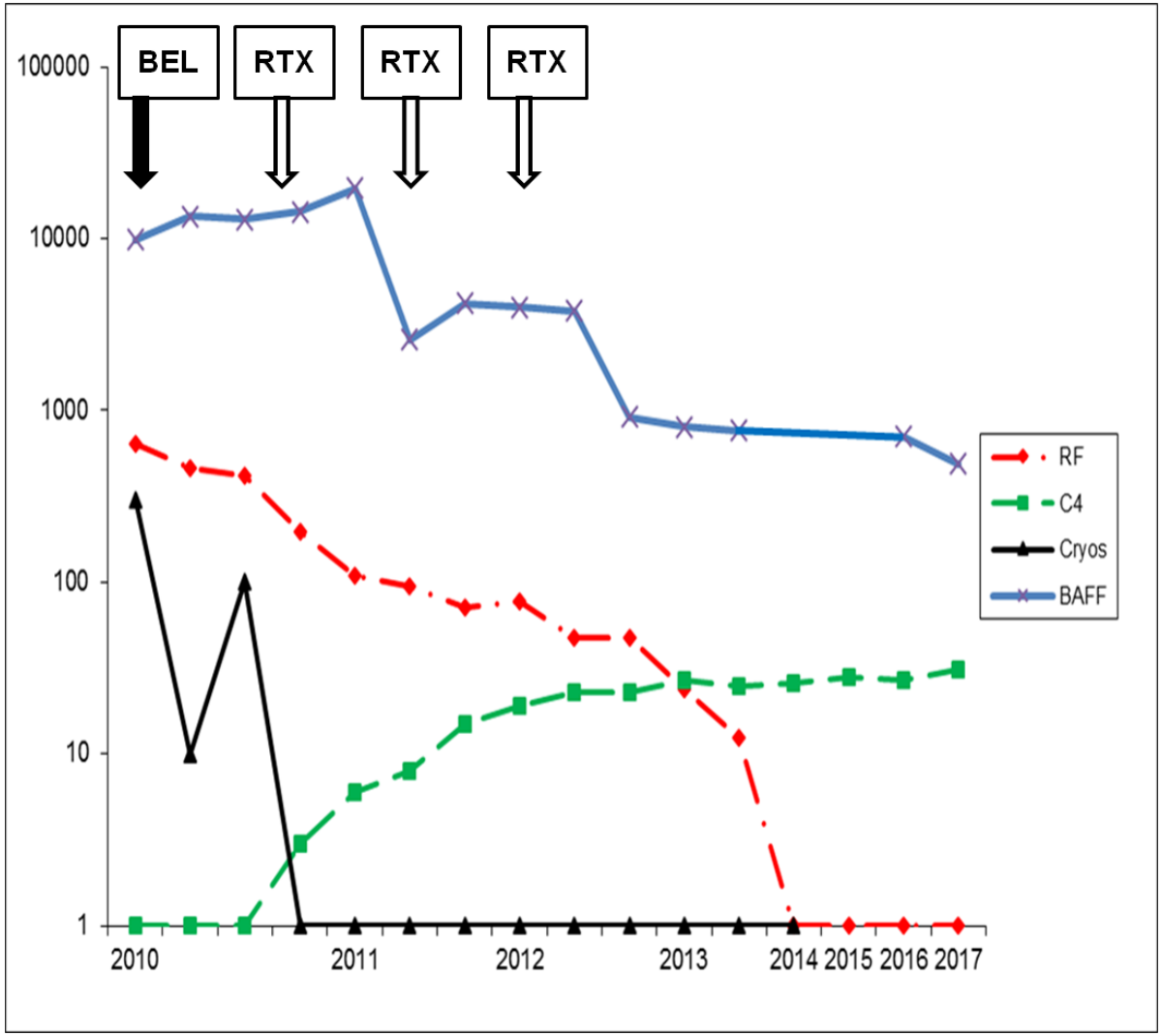


Fig. 2. The course of serum cryoglobulins (mg/dl), rheumatoid factor (IU/ml), C4 (mg/dl), and serum BAFF (pg/ml) after sequential belimumab/rituximab therapy.

Treat to target both **microenvironment and B lymphocyte**

	2010, Jun.	2010, Nov.	2011, Jul.	2012, Jan.	2013, Oct.	2014, Nov.	2015, Aug.	2016, May	2017, Sept
	BEL Pre/Post	**RTX** Pre/Post	**RTX** Pre/Post	**RTX** Pre/Post	**WITHOUT THERAPY**				
Clinic									
Parotid Swelling	+/+ 25 mm/24 mm	+/↓ 24 mm/18 mm	↓/↓↓ 18 mm/13 mm	↓↓/- 13 mm/7,5 mm	-	-	-	-	-
Vasculitic Skin Ulcer	+/+	+/↓↓	↓↓/↓	-/-	-	-	-	-	-
Peripheral neuropathy	+/+	+/+	+/+	+/+	+	+	+	+	±
Histology									
Lip Biopsy	Low grade MALT B-NHL		Sialadenitis Focus Score 1,648	Sialadenitis Focus Score 0,759					
Laboratory									
Cryoglobulins	+/-	+/-	-/-	-/-	-	-	-	-	-
RF (IU/L)	638/413	413/109	95/77	72/-	-	-	-	-	-
Serum monoclonal component	IgM k/IgM k	IgM k/IgM k	IgM k/-	-/-	-	-	-	-	-
C4 (mg/dL)	0/1	1/6	8/15	19/25	40	26	28	27	31
BAFF (pg/mL)	13512/13064	14271/19580	2580/4194	2058/918	759				490
IgG (mg/dL)	1529/1128	1128/895	851/838	862/787	811	872	892	783	732
IgA (mg/dL)	254/213	213/192	188/192	197/172	158	132	238	114	121
IgM (mg/dL)	295/157	157/52	51/40	35/5	2	5	6	6	6
Blood B cells ($CD19^+$)	33%/11%	11%/0	0/0	0/0	0	0	0	0	0
ANA titre	1:1280	1:1280	1:1280	1:640	1:640	1:640	1:640	1:320	1:320
Anti-SSA/SSB Abs	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+

2017, submitted



2017, submitted

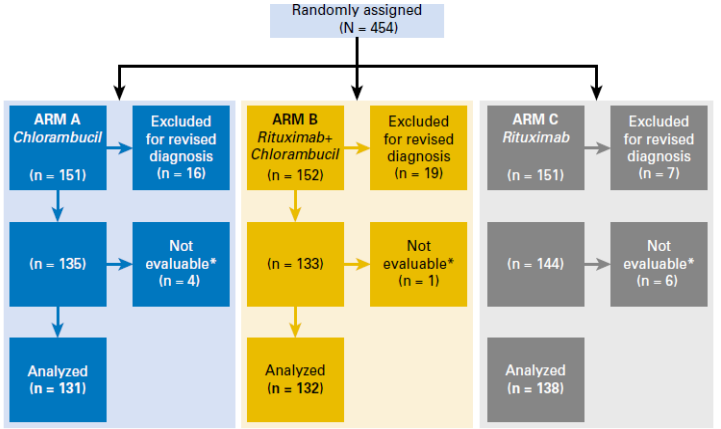
VOLUME 35 · NUMBER 17 · JUNE 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Final Results of the IELSG-19 Randomized Trial of Mucosa-Associated Lymphoid Tissue Lymphoma: Improved Event-Free and Progression-Free Survival With Rituximab Plus Chlorambucil Versus Either Chlorambucil or Rituximab Monotherapy

Emanuele Zucca, Annarita Conconi, Giovanni Martinelli, Reda Bouabdallah, Alessandra Tucci, Umberto Vitolo, Maurizio Martelli, Ruth Pettengell, Gilles Salles, Catherine Sebban, Armando Lopez Guillermo, Graziella Pinotti, Liliana Devizzi, Franck Morschhauser, Hervé Tilly, Valter Torri, Stefan Hohaus, Andrés J.M. Ferreri, Pierre Zachée, André Bosly, Corinne Haioun, Caterina Stelitano, Monica Bellei, Maurilio Ponzoni, Anne Moreau, Andrew Jack, Elias Campo, Luca Mazzucchelli, Franco Cavalli, Peter Johnson, and Catherine Thieblemont



* 11 patients were not evaluable: 7 never treated, 4 because of major protocol violations

Results

At a median follow-up of 7.4 years, addition of rituximab to chlorambucil led to significantly better EFS (hazard ratio, 0.54; 95% CI, 0.38 to 0.77). EFS at 5 years was 51% (95% CI, 42 to 60) with chlorambucil alone, 50% (95% CI, 42 to 59) with rituximab alone, and 68% (95% CI, 60 to 76) with the combination (P = .0009). Progression-free survival was also significantly better with the combination (P = .0119). Five-year overall survival was approximately 90% in each arm. All treatments were well tolerated. No unexpected toxicities were recorded.

Conclusion

Rituximab in combination with chlorambucil demonstrated superior efficacy in mucosa-associated lymphoid tissue lymphoma; however, improvements in EFS and progression-free survival did not translate into longer overall survival.

Extranodal sites ≥ 2	123 (30.7)
Nodal involvement	142 (35.4)
Bone marrow involvement	71 (17.7)
Prior local therapy†	32 (8.0)
Primary gastric site‡	171 (42.6)

As the only randomized study that has specifically addressed MALT lymphoma, these results can be considered a benchmark for future trials in this entity. Lack of OS difference between arms has also provided evidence for the use of rituximab alone as initial therapy to delay or avoid the long-term risks of chemotherapy and radiotherapy.

THE LANCET
Haematology

Volume 1, Issue 3, December 2014, Pages e104-e111

Articles

First-line response-adapted treatment with the combination of bendamustine and rituximab in patients with mucosa-associated lymphoid tissue lymphoma (MALT2008-01): a multicentre, single-arm, phase 2 trial

Dr Antonio Salar MD [a], Eva Domingo-Domenech MD [c], Carlos Panizo MD [d], Concepción Nicolás MD [e], Joan Bargay MD [f], Ana Muntañola MD [g], Miguel Canales MD [h], José Luis Bello MD [i], Juan Manuel Sancho MD [j], José Francisco Tomás MD [k], María José Rodríguez MD [l], Francisco Javier Peñalver MD [m], Carlos Grande MD [n], José Javier Sánchez-Blanco MD [o], Luis Palomera MD [p], Reyes Arranz MD [q], Prof Eulogio Conde MD [r], Mar García MD [b] … Carlos Montalbán MD [k, u]

- Multicenter, single-arm, non randomised, phase II trial
- 57 pts
- Median follow-up 43 months
- EFS at 4 years was 88% (95% CI 74–95).

Take-home messages

• Lymphoma is the main cause of **mortality** in SS pts.

• Persistent glandular swelling and cryoglobulins/CV are **pre-lymphomatous conditions** in SS and their appearance is a **red flag** for higher risk of lymphoma development.

In this context, lymphoma presence must be ruled out.

Biopsy is crucial for both for diagnostic and prognostic purposes.

• **Adverse predictor factors** are available and may help to stratify pts on the basis of their lymphoproliferative risk.

• The **study of etiopathogenesis** and **the individuation of new biomarkers** in SS are definitely worthwhile to improve the **stratification of patients** in order to give a **valid and effective therapy for SS** in the next future, hopefully preventing the evolution towards malignant lymphoproliferation.