

Current limitations and ongoing initiatives to evaluate the activity, damage and outcome of primary Sjögren's syndrome

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The current methodologies to assess the activity, damage and outcome of primary Sjögren's syndrome (pSS) are insufficient: novel indexes and biomarkers are current unmet needs to this end. Several cooperative research initiatives are then ongoing, such as the HarmonicSS project (European Union Grant 731944; <https://harmonicss.eu>) (1), the BIG DATA Sjögren project (2), the PRECISESADS (European Union Grant 115165; <https://www.precisesads.eu>) and the NECESSITY (European Union Grant 806975).

For what concerns disease activity, during the last International Meeting on pSS held in Washington DC, USA, April 2018 (3), it was clearly pointed out that many pSS patients, who indeed might benefit from novel therapies, can not undergo clinical trials due the lack of positive inclusion criteria. In fact, these often imply at least a moderate pSS activity as evaluated by the only composite index presently available in pSS, *i.e.* the ESSDAI (4). This index may be however insufficient, alone, for this purpose (5).

With regards to damage in pSS, the possible accumulation of it during the disease course is still poorly investigated and captured, and salivary gland ultrasound (SGUS) is a promising tool to overcome this issue (6-9). However, as currently evaluated in pSS, SGUS abnormalities possibly related either to activity or to damage are grouped in the same final score, then with major limitations to clearly differentiate these two causes of glandular impairment (10).

Thirdly, it is still not possible, at present, to predict the course of pSS at the beginning of the disease, *i.e.* at the time of the first manifestations or definite diagnosis. Efforts are required, in particular, for the most important disease manifestation which impacts on patient survival, *i.e.* the possible development

of malignant lymphoma. In addition, manifestations which may follow the worsening of lymphoproliferation, rather than being true lymphoma predictors, must be distinguished.

The evaluation of disease activity of pSS is currently based on the sole ESSDAI score. This is a composite index similar to other indexes for disease activity in connective tissue diseases, such as SLEDAI in systemic lupus erythematosus. The major contribution to the final ESSDAI score is given by the systemic features of pSS, a number of which, however, are not frequent in this disease (4). Lupus is a systemic disease quite different from pSS. The pathobiologic and phenotypic essence of pSS is, in fact, glandular inflammation and lymphoproliferation, leading to mucosal dryness and to the increased risk of lymphoma evolution (5, 11, 12). These key disease features however contribute more limitedly to ESSDAI. Consistently, the majority of patients with pSS mainly suffer from sicca symptoms, fatigue and other constitutional symptoms, but show only a mild disease activity as evaluated by ESSDAI. However, about one third of pSS-related lymphomas occur in patients having such a low ESSDAI score at baseline (5, 13, 14), even if it is conceivable that a higher disease activity may predispose to a higher risk of lymphoma. Then, the question is what is really disease activity in pSS, and, in turn, if it was properly measured up to now. Also patients with a low ESSDAI may indeed suffer from a higher disease activity, as witnessed by key biological, pathological and clinical features. Such higher disease activity, pSS-related, should then be caught by means of an index different from ESSDAI.

The essence of pSS was very well summarised by Talal *et al.* (15) and then by Moutsopoulos (11), who pointed

their attention to the autoimmune and lymphoproliferative disorder, and to autoimmune epithelitis. Inflammation and lymphoproliferation of glandular MALT is the hallmark of pSS, reflects the biologic activity, and in turn leads to major pSS clinical features, *i.e.* sicca syndrome and to the increased risk of B-cell malignancy. An index outweighing pSS systemic disease features, and not the inflammation and lymphoproliferation within MALT, may be then insufficient, alone, to assess disease activity. Very recently, within the HarmonicSS EU-funded multicentre research project, one additional composite index to evaluate pSS activity, focused on the inflammatory and lymphoproliferative MALT involvement, was proposed. This index will be developed based on histopathology as the golden standard for the definition of the extent and quality of pSS-related glandular inflammation and lymphoproliferation (as reflected, for instance, by the focus score, the presence of germinal centres, of lymphoepithelial lesions, and of tissue B-cell clonal expansion). Thus, histopathology and tissue analyses remain fundamental. One novel development is, however, also to investigate, within the large number and harmonised pSS patients, whether “surrogates” of histopathology exist, *i.e.* the clinical, laboratory and imaging abnormalities significantly correlated with tissue alterations. Based on current knowledge this seems possible, and surrogates might include persistent salivary gland swelling and cryoglobulinemic vasculitis (clinical features), cryoglobulinaemia, rheumatoid factor positivity and its titre, low C4, beta2 microglobulin, immunoglobulin free light chains and biomarkers in biologic fluids (laboratory features), and SGUS abnormalities (imaging feature). Finally, the composite index, based both on tissue/biopic and surrogate items, will be developed. The hope is that this index might represent one additional and rather simple tool to evaluate disease activity in pSS, not exclusively dependant on tissue biopsy. In addition, this approach could be further enriched by the improved detection of disease biomarkers in the next future.

The accumulation of damage in pSS is conceivably linked to antedating glandular inflammation, causing subsequent irreversible lesions, fibrotic or fatty, with loss of functional parenchyma. On the other hand, tissue damage may also progress in part disconnected from activity. In rheumatoid arthritis, for instance, bone erosions may progress also independently from active synovitis (16). Then, pathologic events leading to glandular fibrosis, decrease in glandular parenchyma, and adipose substitution, rather than to inflammation, may be prominent in the single predisposed individual. Overall, a major need in pSS is not only the improved evaluation of disease activity, but also of glandular damage, which should be separately scored. Of note, data on repeated salivary gland biopsy during the course of pSS are scanty, and changes in both glandular inflammation and in glandular damage may occur (17, 18). It is unlikely that the progression of tissue damage in pSS will be adequately investigated by the sole salivary biopsy, since: i) biopsy is a rather invasive tool, which cannot be easily repeated in the follow-up; and ii) it does not allow an extensive evaluation of the pathologic process, since only a limited number of glandular lobules are examined, within a pathologic process that may be diverse in different anatomical areas (18). The possible existence of different subsets pSS patients (19), and their better definition, *i.e.* disease stratification, is under investigation. It might better dissect those patients more prone to accumulate glandular damage over time. SGUS will likely become important to this end in the next future. This tool allows an extensive visualisation of the major salivary glands, may be easily repeated over time, and can detect lesions related both to activity and to damage (5, 6, 8). The use of image segmentation, automatic scoring (thus facilitating reliability) and artificial intelligence applied to SGUS in pSS is in course within a dedicated HarmonicSS task, and glandular damage is being evaluated separately (9, 20). Saliva analysis represents another approach to detect biomarkers of both salivary inflammation and damage (21).

A third unmet need in pSS is finally to improve the prediction of the course of the disease at the beginning of the follow-up. Extensive research is again in course to this end, and a careful clinical characterisation and patient stratification is a key preliminary step. Different predictors may then be found in different patient subsets. This concept was underlined at last pSS International Meeting, Washington D.C., USA, 2018. Disease stratification is indeed the primary goal of the largest funded multicentre research in pSS currently ongoing, *i.e.* the EU-Horizon 2020 HarmonicSS project. The issue of predicting the risk of lymphoma in pSS, based on patient harmonisation and stratification, is a good example within HarmonicSS.

Many lymphoma predictors have been highlighted in pSS (22, 23). The more important ones appear persistent salivary gland swelling and cryoglobulinaemia (5), which are related each other and in turn are strictly related to other predictors, as cryoglobulinaemia-associated features (glomerulonephritis, peripheral neuropathy), a heavier involvement of MALT by salivary gland (SG) biopsy, and laboratory features as low C4, monoclonal gammopathy and rheumatoid factor-related peculiar idiotypes (22-25). Many other predictors have been also suggested, such as lymphadenopathy, splenomegaly, neutropenia, lymphopenia, free immunoglobulin light chains, increased serum beta2 microglobulin, positive rheumatoid factor in general, genetic abnormalities, oncogenetic events, cytokines and growth factors, chemokines, and ongoing monoclonal B-cell expansion in metachronous tissue biopsies (22-25). Several so called “predictors” might, rather, relate to the progression of the bulk of B-cell lymphoproliferation and/or to partial B-cell deregulation or oncogenetic events, still insufficient to lead to a definite B-cell malignancy. Thus, their distinction is relevant. The composite ESSDAI score, which includes a number of lymphoma-unrelated or poorly-related items, does not appear as a true predictor by itself: it is related to true predictors included in the score itself (salivary swelling and cryoglobulinae-

mia), and seems to follow lymphoma evolution (5, 13, 14).

In addition, even if a given true predictor is present, a further dissection may be required. For instance, only some of the pSS patients with persistent glandular swelling develop lymphoma, and the presence of additional risk factors appears relevant for the prediction of the final increased risk (26). Finally, lymphoma prediction should be repeated. In fact, the risk of lymphoma evolution may change over time and then a dynamic approach, requiring the re-evaluation of the lymphoma risk at any follow-up visit, is indicated.

Within the HarmonicSS project, a large number of pSS cases with lymphoma will be included, allowing an extensive evaluation of the risk and of the role of follow-up. Already proposed lymphoma prediction models will be re-evaluated in harmonised pSS cohorts, and novel prediction models will be developed. In general, pSS harmonisation and stratification is relevant for outcome prediction studies in pSS.

In summary, three major unmet needs in pSS, today, are represented by the improved evaluation of disease activity, of damage and of outcome. Active collaborative research is ongoing to this end, and many novel therapeutic opportunities now available (27) could be then better investigated.

References

1. KOUROU KD, PEZOULAS VC, GEORGA EI *et al.*: Cohort Harmonization and Integrative Analysis From a Biomedical Engineering Perspective. *IEEE Rev Biomed Eng* 2019; 12: 303-18.
2. BRITO-ZERON P, ACAR-DENIZLI N, ZEHER M *et al.*: Influence of geolocation and ethnicity on the phenotypic expression of primary Sjögren's syndrome at diagnosis in 8310 patients: a cross-sectional study from the Big Data Sjögren Project Consortium. *Ann Rheum Dis* 2017; 76: 1042-50.
3. BOMBARDIERI M, BALDINI C, ALEVIZOS I *et al.*: Highlights of the 14th International Symposium in Sjögren's Syndrome. *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S3-13.
4. SEROR R, RAVAUD P, BOWMAN SJ *et al.*: EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. *Ann Rheum Dis* 2010; 69: 1103-9.
5. DE VITA S, GANDOLFO S, ZANDONELLA CALLEGHER S *et al.*: The evaluation of disease activity in Sjögren's syndrome based on the degree of MALT involvement: glandular swelling and cryoglobulinaemia compared to ESSDAI in a cohort study. *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S150-6.
6. DE VITA S, LORENZON G, ROSSI G *et al.*: Salivary gland echography in primary and secondary Sjögren's syndrome. *Clin Exp Rheumatol* 1992; 10: 351-6.
7. BALDINI C, ZABOTTI A, FILIPOVIC N *et al.*: Imaging in primary Sjögren's syndrome: the 'obsolete and the new'. *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S215-21.
8. ARGYROPOULOU OD, VALENTINI E, FERRO F *et al.*: One year in review 2018: Sjögren's syndrome. *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S14-26.
9. ZABOTTI A, ZANDONELLA CALLEGHER S, GANDOLFO S *et al.*: Hyperechoic bands detected by salivary gland ultrasonography are related to salivary impairment established Sjögren's syndrome. *Clin Exp Rheumatol* 2019; 37 (Suppl. 118): S146-52.
10. DEVAUCHELLE-PENSEC V, ZABOTTI A, CARVA-JAL-ALEGRIA G, FILIPOVIC N, JOUSSE-JOULIN S, DE VITA S: Salivary gland ultrasonography in primary Sjögren's syndrome: opportunities and challenges. *Rheumatology (Oxford)* 2019 Mar 19 [Epub ahead of print].
11. MOUTSOPOULOS HM: Sjögren's syndrome: autoimmune epithelitis. *Clin Immunol Immunopathol* 1994; 72: 162-5.
12. TZIOUFAS AG, KAPSOGEOGOU EK, MOUTSOPOULOS HM: Pathogenesis of Sjögren's syndrome: what we know and what we should learn. *J Autoimmun* 2012; 39: 4-8.
13. FRAGKIOUDAKI S, MAVRAGANI CP, MOUTSOPOULOS HM: Predicting the risk for lymphoma development in Sjögren's syndrome: An easy tool for clinical use. *Medicine* 2016; 95: e3766.
14. RETAMOZO S, GHEITASI H, QUARTUCCIO L *et al.*: Cryoglobulinaemic vasculitis at diagnosis predicts mortality in primary Sjögren's syndrome: analysis of 515 patients. *Rheumatology (Oxford)*. 2016; 55: 1443-51.
15. TALAL N, BUNIM JJ: The development of malignant lymphoma in the course of Sjögren's syndrome. *Am J Med* 1964; 36: 529-40.
16. VILLENEUVE E, HARAOU B: Uncoupling of disease activity and structural damage. Does it matter clinically? *Ann Rheum Dis* 2013; 72: 1-2.
17. JONSSON R, KRONELD U, BACKMAN K *et al.*: Progression of sialadenitis in Sjögren's syndrome. *Br J Rheumatol* 1993; 32: 578-81.
18. FISHER BA, JONSSON R, DANIELS T *et al.*: Standardisation of labial salivary gland histopathology in clinical trials in primary Sjögren's syndrome. *Ann Rheum Dis* 2017; 76: 1161-8.
19. BRITO-ZERÓN P, ACAR-DENIZLI N, NG WF *et al.*: How immunological profile drives clinical phenotype of primary Sjögren's syndrome at diagnosis: analysis of 10,500 patients (Sjögren Big Data Project). *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S102-12.
20. VUKICEVIC AM, MILIC V, ZABOTTI A *et al.*: Radiomics-based assessment of primary Sjögren's syndrome from salivary gland ultrasonography images. *J Biomed Health Inform* 2019 (in press).
21. GALLO A, VELLA S, TUZZOLINO F *et al.*: miRNA-mediated regulation of Mucin-type O-Glycosylation pathway: a putative mechanism of salivary gland dysfunction in Sjögren's syndrome. *J Rheumatol* 2019 Mar 1. [Epub ahead of print].
22. DE VITA S, GANDOLFO S: Predicting lymphoma development in patients with Sjögren's syndrome. *Expert Rev Clin Immunol* 2019 (in press).
23. GOULES AV, TZIOUFAS AG: Lymphomagenesis in Sjögren's syndrome: Predictive biomarkers towards precision medicine. *Autoimmun Rev* 2019; 18:137-43.
24. MIKLOS JA, SWERDLOW SH, BAHLER DW: Salivary gland mucosa-associated lymphoid tissue lymphoma immunoglobulin V(H) genes show frequent use of V1-69 with distinctive CDR3 features. *Blood* 2000; 95: 3878-84.
25. DE VITA S, QUARTUCCIO L, SALVIN S *et al.*: 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. *Clin Exp Rheumatol* 2014; 32: 490-4.
26. QUARTUCCIO L, ISOLA M, BALDINI C *et al.*: Biomarkers of lymphoma in Sjögren's syndrome and evaluation of the lymphoma risk in prelymphomatous conditions: results of a multicenter study. *J Autoimmun* 2014; 51: 75-80.
27. GANDOLFO S, DE VITA S: Emerging drugs for Sjögren's syndrome. *Expert Opin Emerg Drugs* 2019; 24: 121-32.