Highlights of the 15th International Symposium on Sjögren's Syndrome

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The 15th International Sjögren's Symposium (ISSS) was held in Rome, Italy, between the 7th and 10th of September 2022, and was chaired by Salvatore de Vita (Udine, Italy) and co-chaired by Chiara Baldini (Pisa, Italy) and Luca Quartuccio (Udine, Italy). The programme covered recent developments in pathogenesis, clinical assessment with stratification, lymphoproliferation, and personalised medicine. The discussion also focused on the nomenclature of Sjögren's syndrome (SS) and the implications of COVID-19 infection. One of the main themes of the Symposium was the evaluation and understanding of the pathogenesis of SS associated with other autoimmune diseases, and on how different medical specialists and primary care physicians could better coordinate with each other in dealing with patients and in the field of research. The needs and opinions of patients were another key topic of discussion, with the participation of representatives from European and US Associations, with different health policies applying in different countries. Discussion on recent developments in treatment and testing of new drugs, together with International cooperative research was also encouraged and promoted.

The Symposium was a hybrid event with more than 300 participants from all over the world. Travel grants were awarded to 35 young investigators and post-doc- toral fellows, enabling them to present their work, exchange ideas and network with more senior investigators. There were 34 oral and 157 poster presentations in addition to 78 plenary lectures. The meeting was preceded by a pre-Conference Workshop on Salivary Gland Ultrasonography in SS that combined didactic and practical training sessions.

The opening lecture by M. Ponzoni (Milan, Italy) focused on autoimmunity and infections in marginal zone B-cell lymphomas. Marginal zone B-cell lymphomas (MZLs) are a group of clinically indolent B-cell lymphomas postulated to derive from memory B lymphocytes in the 'marginal zone' of secondary lymphoid tissue. MZLs encompass distinct entities including mucosa-associated lymphoid tissue (MALT) lymphoma. These lymphomas are frequently associated with chronic antigenic stimulation represented either by infectious agents, particularly bacteria and viruses, or autoimmune diseases as exemplified by SS, Hashimoto thyroiditis, and newly recognised IgG4-related disease. In his lecture, Ponzoni specifically pointed out the pathogenetic role of several infectious agents including *Helicobacter Pylori* in gastric lymphoma; *Borrelia sp* in skin lymphoma, *Campylobacter jenuni* in immunoproliferative small intestinal disease (IPSID), *Chlamydia psittaci* in ocular adnexal lymphomas; *Achromobacter* in lung MZL; *Haemophilus influenzae* in paediatric nodal MZ lymphoadenopathy and *Moraxella Catarralis* in Hodgkin lymphoma, lymphocytic predominance.

First plenary session

Looking more closely at the programme of the Symposium, the first plenary session was dedicated to the evolving topics in the pathogenesis of pSS. The focus of this session was to showcase the most relevant novel findings in the pathogenesis of pSS, with a focus ranging from the role of epithelial cells and innate immunity to the importance of adaptive immune responses and B/T cell crosstalk in lymphomagenesis.

E.K. Kapsogeorgou (Athens, Greece) reported novel findings on the role of salivary gland ductal epithelial cells (SGECs) in contributing to the Sjogren's pathogenesis, a disease also known as "autoimmune epithelitis" given the importance of this cell type. She

highlighted the importance of several immune receptors expressed by SGECs from those sensing pathogens (Toll-like receptors in particular) to costimulatory molecules (CD40, ICOS-L, CD86, MHC-II) able to directly interact with immune cells. Interestingly, SGECs display higher molecular weight CD86 compared to B cells, a result of different N-glycosylation patterns which may impact on positive *versus* negative regulatory signals. SGECs are also a known source of critical autoantigens in pSS, whereby the release of exosomes as well as epigenetic abnormalities resulting in dysregulated DNA methylation can increase the expression of autoantigens, among which La/SSB thus contributing to the maintenance of autoimmunity.

G. Nocturne (Paris, France) further explored the capability of SGECs to interact with immune cells, with particular focus on the cross-talk with T cells and B cells. With regard to B cells, SGECs are capable of providing critical survival and activating signals such as BAFF, APRIL, IL-6 and CXCL12 and the co-culture of SGECs and B cells results in enhanced B cell survival and differentiation into plasmablasts acquiring CD38 expression. This effect can be further potentiated by stimulation with TLR3 ligands and type-I IFN while incubation with BTK or PI3K inhibitors can downregulate B cell activation over and above the dual blockade of BAFF/APRIL. With regard to T cells, costimulatory molecules displayed by SGECs, as described above, can directly induce phenotypic changes in CD4 T cells, and in particular induce the differentiation of CD4 T cell subsets such as T-follicular helper (Tfh) cells and T-peripheral helper (Tph) cells which have been shown to provide help to B cells at follicular and extrafollicular sites (further discussed below). In addition to costimulatory pathways, a novel role for SGEC-derived IL-7 was reported, with evidence that in SGEC/T cell co-cultures, IL-7 can directly induce IFN-γ in T cells, which in turn leads to SGEC activation, an effect which is lost upon IL-7 blockade.

M.A. Versnel (Rotterdam, The Netherlands) further highlighted the importance of type I IFN in pSS. She reported novel data showing that an increase in type-I IFN family, which includes 17 subtypes, can be observed in the serum of between 50–85% of pSS patients when measured using ultrasensitive fluorescent bead technology showing a high degree of correlation with type-I IFN signatures identified using RNASeq on peripheral blood. Interestingly, the type-I IFN signature in pSS is associated with the biological and haematological domains of ESSDAI, RF and systemic complications at the 5-year follow-up. Type-I IFN is typically dependent on the activation of innate immune cells, and in particular plasmacytoid dendritic cells (pDCs). Depletion of pDCs in murine models of pSS, such as NOD mice, results in disease amelioration with improvement in secretory function. Although innate immunity is not associated with antigen-specific immunological memory, unlike adaptive immunity, there is increasing evidence that innate immune cells can display epigenetic and metabolic (*i.e.* glucose/cholesterol metabolism) reprogramming that can be induced by the inflammatory milieu and retained as a non-antigen specific "trained memory". In this regard, type-I IFN seems to play an important role in training immune cells to retain an activated state associated with the release of pro-inflammatory mediators, including CCL2, which appears to be associated with cardiovascular events in the UK pSS registry.

Type-I IFNs are typically induced by engagement with particular TLRs (TLR3, TLR7, TLR9) activated by intracellular pathogens and viral infections, which have been long associated with predisposition to pSS although no definitive causative link has been demonstrated as yet. In this context, M. Wahren-Herlenius (Stockholm, Sweden) reported interesting novel, albeit indirect, data related to infection rates and predisposition to pSS from nationwide clinical records of inpatients and outpatients obtained between 1987 and 2014. From a cohort of 960 pSS patients and over 9,000 controls, the observed rate of infections was 21% in pSS compared to 12% of controls, giving a 2.0 odds ratio rising to 2.7 in anti-SSA+ patients. Of relevance, respiratory tract and skin infections but not gastrointestinal tract infections were associated with pSS.

Switching to adaptive immunity in the pathogenesis of pSS, G. Verstappen (Groningen, The Netherlands) presented interesting data with regard to the transcriptomic profile of B cells infiltrating the SG. Through bulk RNASeq they identified different B cell subsets characterised by unique gene signatures, ranging from classical germinal-centre (GC) B cells expressing AICDA, BTK, Serpin-9 to a novel subset of FcRL4+ B cells which locate at extrafollicular sites. These FcRL4+ B cells display a phenotype similar to double-negative (DN, *i.e.* lacking expression of IgD and CD27) B cells and appear to respond to a CXCR3/CXCL10 chemokine gradient and are able to infiltrate pre-malignant lympho-epithelial lesions (LEL) where they can undergo clonal expansion. Following on follicular *versus* extrafollicular responses in the SG, M. Bombardieri (London, UK) focused on costimulatory pathways involved in the cross-talk between T and B cells in the SG and their relevance to the formation of ectopic germinal centres and evolution to MALT lymphoma. In addition to traditional T CXCR5+PD1+ICOS+ T follicular helper cells (Tfh), which are capable of migrating towards B cell follicles through CXCL13 chemokine gradients contributing to the ectopic GC response, recent data highlighted the importance of the novel subset of T-peripheral helper cells (Tph) in promoting B cell help at extrafollicular sites. Tph, characterised by a CXCR5-PD1hiICOS+ phenotype is equally capable of producing high levels of IL-21, a key cytokine involved in B cell activation, but can also produce CXCL13, suggesting un upstream role in ectopic GC formation. Tph cells, possibly migrating in the SG through a CCL25/CCR9 pathway appear uniquely positioned to sustain extrafollicular B cell responses which are intimately involved in B cell lymphomagenesis.

Among other pathogenic properties in pSS, autoreactive B cells give rise to high levels of locally produced and cir-

culating autoantibodies which can be measured in the serum. Torsten Witte (Hannover, Germany) presented novel autoantibody specificities detected using a novel Luminex Antigen Array capable of measuring over 7,000 autoantigens simultaneously. Preliminary data on sera from >100 pSS patients, ~80% of which anti-Ro/SSA+, highlighted the presence of autoantibodies associated with extra-glandular manifestations, including specificities more frequently observed in patients with lung involvement and peripheral neuropathy. Further validation will confirm the clinical utility of these autoantibodies in clustering patients with distinct clinical phenotypes.

Closing the pathogenesis session, C.J. Lessard (Oklahoma City, USA) presented novel key findings on genetic and epigenetic factors associated with increased susceptibility to pSS. Polygenic Risk Scores provided a cumulative estimate of the effect that many genetic variants have on an individual's susceptibility to develop a particular disease and are typically calculated as a weighted sum of trait-associated alleles. In this context, some genetic variants including HLA, IRF5-TNPO3 and STAT4 appear exclusively associated with the anti-Ro/SSA+ subset of pSS, while others are similarly distributed among seropositive and seronegative patients. Long non-coding RNAs (lncRNAs) are a functionally diverse class of non-protein coding RNAs that are longer than 200 nucleotides. LINC01871 was found to be overexpressed in pSS compared to controls and appears to be linked to perturbation of T cell activation in pSS. LINC01871 is implicated in T cell pathways and TCR signalling; accordingly, anti-CD3/CD28 engagement on T cells resulted in decreased LINC01871 expression, an effect which was abrogated by calcineurin inhibition.

Second plenary session

The second plenary session of the Symposium was dedicated to the Evolving topics in pSS stratification. The leitmotiv of this session was the recognition of the different subtypes of the disease and their impact on SS diagnosis and treatment. The session was subdivided in three different parts. The first part focused on the relevance of clinical phenotyping in pSS stratification. A.G. Goules (Athens, Greece) presented the harmonised research data of 7551 patients recruited from 20 European Cohorts in the HarmonicSS Consortium. Specifically, patients were stratified according to gender, age at pSS onset/diagnosis (<35 or >65 yrs), autoantibodies (*i.e.* triple, quadruple seronegative and cryoglobulin positive) and geolocalisation. Important differences in the frequency of glandular and extra-glandular disease manifestations emerged from the comparison of the different groups largely confirming the 2nd wave spontaneous multicentre research data emerged inside the HarmonicSS project. Regarding lymphoma development, when compared to females, male patients presented a higher frequency of diffuse large B cell lymphomas (DLBCL). Triple and quadruple negative patients had lower frequency of MALT lymphoma whereas by contrast patients with cryoglobulin positivity and patients from southern countries presented a higher frequency of MALT lymphoma along with a higher prevalence of glomerulopathy, small airway disease, peripheral nervous disease and palpable purpura.

In the following part of the session the usefulness of the laboratory biomarkers in pSS patient stratification was presented. J.-O. Pers (Brest, France) summarised the recent data from the PRECISESADS Clinical Consortium (1) presenting a molecular classification scheme based on the multi-omic profiling of whole blood samples from a European cohort of over 300 patients, and a similar number of age and gender-matched healthy volunteers (HV). The authors identified 4 groups of patients with distinct patterns of immune dysregulation. Cluster 1 (C1), C3 and C4 displayed a high IFN signature with various Type I and II IFN gene enrichment. C1 had the strongest IFN signature with both Type I and Type II gene enrichment whereas C4 had a Type II gene enrichment stronger than Type I and C3 had the opposite composition. C2 exhibits a weak Type I and Type II IFN signature resembling HV. Moreover, C1 patients presented a high prevalence of SNPs, C3 patients a more prominent B cell component while C4 patients had an inflammatory signature driven by monocytes and neutrophils, together with an aberrant methylation status. In addition, in this session, original data obtained from analysing glandular architecture and inflammatory infiltrate of minor salivary gland (MSG) by imaging mass cytometry (IMC) were presented. The authors showed that the cell subpopulations in the inflammatory infiltrates varied between patients with different lesion severity including SS related mucosa-associated lymphoid tissue (MALT). Switched memory B cells appeared as prominent in intermediate and severe infiltrates. These switched memory B cells were associated with 3 types of B cell subsets: 1. naive and innate B cells, 2. double negative CD27- IgD-B cells and 3. lymphoid structure (TLS) B-cells. Infiltrates in lymphoma lesions appeared to be characterised by ki67+ switched memory B cells and Treg subsets expressing Tbet. Finally, IMC showed that IL-7R expression was increased in pSS compared to sicca patients and variations were seen according to the degree of infiltration. IL-7R was mainly found on CD4+ and CD8+ T cells, switched memory and IgD-CD27- double negative B cells and M1 supporting IL-7R targeting as a promising therapeutic strategy in pSS.

J.-E. Gottenberg (Strasbourg, France) highlighted the relevance of blood transcriptomic in characterising the molecular and clinical variability across pSS patients. He showed that IFNγ was significantly associated with clinical and immunological features of pSS disease activity at enrolment, and with increased frequency of systemic complications during the 5-year follow-up. IFNα protein levels were genetically associated with the class II HLA DQ locus and anti-SSA antibody. Replication of the transcriptomic results was performed using 3 independent cohorts (the ASSESS cohort, the Bergen cohort and the Oklahoma cohort) (2). A BTK overexpression in peripheral blood was also demonstrated in the ASSESS co-

hort as a predictive factor for lymphoma development. SLAMF7 expressed by NK cells, plasma cells, activated Cd4 and CD8 T cells and activated B cells is also under investigation. Finally, he also showed the possibility of using transcriptomics for drug repurposing showing that at present 11 drugs (including 2 PI3K inhibitors and one histone deacetylase inhibitor) are potentially able to invert the disease signature thus representing a potential treatment.

At the end of this session, G. Urbanski (San Francisco, USA) presented some preliminary results of the Sjögren's International Collaborative Clinical Alliance Next Generation Studies (SICCA-NextGen). Using previously collected clinical data/biospecimens, and genome-wide genotyping performed on a cohort of 3,514 participants with extremely well characterised phenotypic data, the researchers proposed to define the transcriptomics and epigenetics of SS at the cell and tissue levels. The idea is to enhance the SICCA registry by generating genome-wide DNA methylation and whole-genome sequencing of single-cell mRNA, bulk mRNA, and miRNA thus enabling high impact studies of underlying biologic pathways of SS. Namely SICCA-NextGen aims to explore transcriptomic diversity across subsets of SICCA participants; to explore correlations between omics profiles and signs of severe disease manifestations; and to characterise longitudinal changes in dynamic omic profiles of subsets of SICCA patients. The second plenary session ended with a focus on salivary imaging and biopsy for stratification. C. Baldini (Pisa, Italy) summarised the literature data supporting the value of SGUS in the phenotypic stratification of pSS patients. Indeed, the literature highlights the close association between SGUS abnormal findings and salivary gland histology, anti-Ro/SSA positivity, biological activity as well as global disease activity (ESSDAI), PROs and damage. Interestingly, recent data have pinpointed that milder or moderate/severe SGUS patterns identified different pSS subset; particularly, moderate/severe SGUS abnormalities appeared to be associated with a more severe disease subset and higher disease damage indices. B. Fisher (Birmingham, UK) extensively discussed the key role of labial minor salivary gland biopsy in pSS stratification underlying the importance of the adequacy of the tissue to ensure a representative result. He also discussed the limitation of the focus score (*i.e.* variation in size of foci, based on HE only, interobserver variability) and proposed alternative measures such as the area of infiltration to foster the value of the biopsy for patient stratification. This was particularly relevant when the extent of inflammation has to be used to predict lymphoma. The key take home message was therefore that the application of innovative methodologies hold potential for stratified medicine and determining treatment responses. The last two presentations were dedicated to surgical and US-guided parotid and submandibular biopsy. A. Vissink (Groningen, The Netherlands) described surgical parotid biopsy as a safe procedure with equal morbidity when compared to a labial biopsy. The procedure could be more often performed from the same gland with an easier detection of lymphoepithelial lesions and lymphomas. Vissink particularly recommended using surgical biopsy for routine diagnostics and diffuse swelling and US-guided core biopsy for tumour masses and other well circumscribed swellings within the gland. Both surgical or US-guided core biopsy might be indicated for lymphoma diagnosis. Considering patients stratification, he suggested that when compared to US-guided core biopsies, parotid surgical biopsies had a higher stratification potential because of the amount of the material obtained. He particularly quoted the study by Delli *et al*. showing that a high number of CD20+ B cells/mm^2 may predict responsiveness to rituximab treatment. Alen Zabotti (Udine, Italy) explained the accuracy and safety of US-guided core biopsy for lymphoma diagnosis on the basis of the literature and of a personal experience. He described their recent study comparing the two techniques in 26 pts with suspected lymphoma. In all cases sufficient high-quality tissue was retrieved, the procedure was well tolerated, with no serious and/or persistent complications occurring. He also quoted a recent paper by A. Baer *et al*. obtaining similar results. He also illustrated the patients' perspective on US-guided core biopsy showing a good acceptance of the procedure. Unlike Vissink, he hypothesised that US-guided core biopsy might also be used for the diagnosis of pSS.

Third plenary session

Evolving topics in SS-related lymphoproliferation

This session included invited and selected oral presentations mainly addressing pathogenetic mechanisms underlying lymphomagenesis in SS with particular attention on the utility of parotid gland biopsy for SS and suspected lymphoma diagnosis.

In the first presentation, A.G. Tzioufas (Athens, Greece) initially reported the analysis of clinical features, outcome and predictor factors for different types of lymphoma from a Greek harmonised dataset. The analysis of 121 lymphomas confirmed MALT as the most frequent histologic type (76%), followed by diffuse large B cell (DLBCL) (11%), other types (8%) and nodal lymphoma (7%). Primary SS patients with MALT lymphoma were younger at lymphoma diagnosis and with shorter disease duration between disease and lymphoma diagnosis in comparison to DLBCL cases. Moreover, they were characterised by a better overall survival and event-free survival in terms of disease progression, lymphoma relapse, histologic transformation, need for treatment and death for any cause. For the first time, a real prediction model for MALT lymphoma was presented using data driven approaches. ESSDAI at SS diagnosis, focus score and cryoglobulinemia were identified as independent predictors for MALT lymphoma with cryoglobulinaemia being the best predictive factor (OR: 5.61, CI: 1.17–27.08). These interesting data were confirmed in a subsequent analysis of MALT and DLBCL lymphoma features of patients included in the HarmonicSS dataset. Moreover, a direct comparison between the two histologic types revealed that the MALT

lymphoma had prevalent minor or parotid gland localisation with unexpectedly high rates of bone marrow and regional lymphonode localisation, while DLBCL were clinically expressed by extra-nodal involvement (lung, stomach). Interestingly, a significant prevalence of MALT lymphoma was detected in southern Europe in comparison to the north. Finally, preliminary data of a Lymphoma prediction model (PRECIOUS/Post-HarmonicSS) identified predictive factors for lymphoma at SS diagnosis (rheumatoid factor and total ESSDAI at diagnosis), 3–5 years before lymphoma development (rheumatoid factor) and at lymphoma diagnosis (total ESSDAI).

Then, J. Reed (Sydney, Australia) highlighted local networks and oncogenetic events potentially involved in B cell expansion. More specifically, he discussed a multi-omics approach which may be employed to isolate rare pathogenic rheumatoid factor (RhF) B cells. In this setting, somatic hypermutation of autoantibody V(D)j makes RhF pathogenic and different lymphoma driver mutations were identified in RhF B cells isolated from SS patients with lymphoma. In particular, pathogenic RhF B cells express high CD86 and, interestingly, these somatic mutations may alter treatment response. Finally, a pathogenic RhF development via a cascade of somatic hypermutations was proposed, characterised by acquisition of lymphoma driver mutations by RhF B cells, accumulation of pathogenic V-region mutations and finally secretion of pathogenic autoantibodies which may induce lymphoma risk in these patients. A better understanding of the molecular mechanisms underlying pathways leading to B cell lymphoma in SS would lead to the identification of predictors and key therapeutic targets for lymphoma prevention at the early stage of poly- or oligo-clonal B cell activation. Finally, the importance of RhF B cell mutation in lymphoma development was subsequently highlighted by X. Mariette (Paris, France) who presented original data demonstrating that SS patients with previous lymphoma display a contraction of the RhF repertoire with over-representation of 1–69 clones. Moreover, defective control of B-cell activation by TNAIP3 and TRAF3 abnormalities and original demonstration of higher levels of BAFF-var in patients with marginal zone lymphoma were identified as novel future factors predictive of lymphoma in SS. Finally, a new, easy to assess score for predicting lymphoma was proposed. The Score of Lymphoma risk in Sjögren's syndrome (SCOLYSS) includes 7 items that are very easy to assess in most of the SS cohorts, including recurrent parotid swelling, splenomegaly and/or adenopathy, purpura, lymphopenia, C4 level, RhF and serum monoclonal component. Though still to be validated in large prospective cohorts, this score may help to identify the thresholds of lymphoma risk and, consequently, patients to monitor closely, to analyse risk change over time and may be proposed as primary or secondary end-point in clinical trials.

The second part of this plenary session was dedicated to a face-to-face brief debate regarding the use of parotid biopsy in disease diagnosis and evaluation of salivary gland swelling or areas suspected for lymphoma. Firstly, A. Zabotti (Udine, Italy) addressed the use of parotid biopsy for salivary gland swelling or suspected areas. Specific ultrasonographic (US) features for lymphoma were described and a US pattern at presentation with six or more «suspicious» features significantly increased the probability of lymphoma diagnosis. Moreover, the important role of US-guided core needle biopsy of suspected areas was highlighted by a picture demonstrating the safety of the procedure in an area between 1 cm anterior and 1 cm below the ear lobe to avoid facial nerve injury. Then, T. Dörner (Berlin, Germany) made a critical reappraisal of the importance of minor salivary gland biopsy (SGB) for SS diagnosis. In particular, he highlighted that the procedure is mandatory for histopathologic evaluation of focal glandular inflammatory infiltrate, for differential diagnosis of several pathologic conditions, including sarcoidosis, amyloidosis, IgG4-related disease, and for lymphoma suspicion. Moreover, SGB has limited value in patients with sicca symptoms without immune abnormalities showing a non-specific chronic sialadenitis or sclerosing chronic sialadenitis. On the other hand, M. Voulgarelis (Athens, Greece) discussed the major limits of parotid GB for SS diagnosis. In particular, he highlighted that parotid and minor SGB have similar sensitivity and specificity for SS diagnosis (78% and 86%, respectively). Moreover, parotid gland may contain lymphoid tissue between lobules and lymphoid follicles (intra-parotid lymph nodes) leading to SS misdiagnosis and may be associated with surgical complications, including facial nerve damage, development of salivary fistulae and sialoceles, requiring specialized centres and expertised personnel and equipment. Finally, H. Bootsma (Groningen, The Netherlands) presented interesting results of an original study aimed at comparing histopathologic parameters in addition to focus score between labial and parotid GBs in a cohort of 99 patients with suspected SS. Gland tissue was analysed with Digital Image Analysis by 2 or 3 independent experienced head and neck pathologists. The histopathology of parotid and labial glands showed moderate/fair correlations. Interestingly, labial SGs showed more inflammatory infiltrate but a higher number of CD20+ B cells and germinal centres were detected in parotid glands. Lymphoepithelial lesions were highly specific for SS diagnosis and more severe in parotid glands. The reproducibility of such findings needs to be validated in further studies but these results represent an interesting field to be explored in the histopathologic analysis of SGBs in SS.

Fourth plenary session

The fourth session was dedicated to the novel insights elaborated for the evaluation of pSS. In the first part the importance of creating platforms to collect and share data, all secure but web accessible emerged clearly. T.P. Exarchos (Ioannina, Greece) illustrated the example of the platform utilised in the HarmonicSS project whereas M. Barnes (London, UK) described the data integration platforms used in the Necessity Experience. The integration

between medical doctors and engineers was further reinforced by C.P. Mavragani (Athens, Greece) and D.I. Fotiadis (Ioannina, Greece) in their talk, where they highlighted the need for a hybrid scientist able to combine clinical knowledge with explainable and trustworthy artificial intelligence to address clinical unmet needs. In the third part, an overview on current novel indices to assess activity, damage and disease-related components of chronic pain and fatigue was provided.

L. Quartuccio (Udine, Italy) highlighted the necessity of improving the performance of composite scores extensively discussing the limitations of the ESSDAI both as inclusion criteria (*i.e.* focused on systemic disease rather than glandular disease, overrepresenting articular, glandular and lymphadenopathy and with biological domain B-cell driven) and as a primary endpoint (not including glandular features and glandular function, not distinguishing the effect in individual domains, not including PROs and with great placebo effect). He concluded that multiple secondary endpoints on sub-populations (*i.e.* seronegative) and single clinical manifestations may be required for better translating trial results into clinical practice.

Considering the composite endpoints session, recent disappointing results from randomised placebo-controlled clinical trials in pSS have questioned the fitness for purpose of ESSDAI as the main primary endpoint to assess clinical efficacy of novel therapeutics. Similar to other autoimmune rheumatic diseases in which composite scores have been proved useful in randomised clinical trials to demonstrate clinical improvement, recent efforts from the international community have led to the development and initial validation of novel composite endpoints in pSS.

H. Bootsma (Groningen, The Netherlands), presented CRESS (Composite of Relevant Endpoints for Sjögren's Syndrome) a novel composite score developed in Groningen and based on 5 equally weighted domains (ESSDAI, ESSPRI, objective salivary gland assessment, objective ocular assessment and a biological domain) whereby responders are identified in the presence of a improvement or lack of progression in at least 3 out of 5 items. More specifically, ESSDAI response is defined as lack of clinical activity (clinESSDAI <5), ESSPRI response by a decrease of at least 1 point or 15% from baseline; lacrimal gland domain by Schirmer's test or ocular staining score (OSS), assessed by an increase of at least 5 mm or decrease of at least 2 points, respectively, in patients with abnormal Schirmer's test or OSS at baseline, or, in patients with normal baseline values, assessed by no change to abnormal for both; salivary gland domain, assessed by unstimulated whole saliva flow (increase of at least 25%) or salivary gland ultrasonography (decrease of at least 25%); and serology domain, assessed by rheumatoid factor (decrease of at least 25%) or IgG (decrease of at least 10%). CRESS was originally developed based on the ASAP-III trial and then validated in the 3 randomised placebo controlled, double-blinded studies, the international abatacept trial, the TRACTISS trial (rituximab) and the tocilizumab ETAP trial. In the ASAP-III and TRACTISS trials, CRESS was clearly superior to the original primary endpoint used in each study in demonstrating a significantly higher rate of responders in the active *versus* placebo arm.

R. Seror (Paris, France), presented the development and preliminary validation of STAR (Sjögren's Tool for Assessing Response), a consensual composite score for assessing treatment effect in pSS which was developed as part of the EU-IMI NECESSITY (New clinical endpoints in primary Sjögren's syndrome: an interventional trial based on stratifying patients) consortium. The preliminary STAR composite score is based on the same 5 items of CRESS, but differs from CRESS on the definition of response in some of the domains (*i.e.* clinESSDAI response is assessed by a 3 points improvement from baseline) and the weight given to each item, whereby response to clinESSDAI and ESSPRI items each scores 3 points while response to the other 3 items each score 1 point; a responder is identified based on a score ≥5. STAR was developed based on data from the TEARS and TRACTISS Rituximab trials and retrospectively validated from data made available from a series of "positive", "in between" and "negative" randomised trials in pSS as assessed by the NECESSITY investigators. STAR, similar to CRESS, demonstrated a significant improvement in the capacity to capture responders in the active *versus* placebo arm of both "positive" and "in between" clinical trials, but not in the most widely regarded "negative" studies. Prospective validation of both STAR and CRESS as novel primary endpoints is the main purpose of the NECESSITY randomised clinical trial which recently started recruitment and will recruit 300 pSS patients divided in two cohorts, one with patients with a baseline ESSDAI <5 and one with a baseline ESSDAI ≥5. CRESS is also been currently validated as primary endpoint in a prospective study with Anifrolumab in pSS patients.

Fifth plenary session

Association of SS with other autoimmune diseases: implications for disease biology and management

A. Doria (Padua, Italy) opened this session highlighting the most important features which may help in the identification of SS patients with associated systemic lupus erythematosus (SLE). In particular, patients with overlap SS-SLE may be characterised by higher frequency of photosensitivity, acute/subacute cutaneous lupus, inflammatory muscular and articular involvement, anti-Sm and anti-DNA positivity and hypocomplementaemia in comparison to SS patients. Moreover, recent evidence supports the new 2019 ACR/EULAR classification criteria as valuable tools for distinguishing SLE from SS patients. In the second part of the presentation, attention focused on the characterisation of SS-SLE patients in comparison to SS-non-SLE. As expected, SLE-SS patients display higher prevalence of ocular and oral sicca symptoms as well as positive Schirmer test and impaired whole unstimulated salivary flow in comparison to SLE-non-SS patients. Moreover, SLE-SS patients present older age at SLE onset, higher risk of peripheral neuropathy,

Raynaud phenomenon and oral ulcers but lower prevalence of renal involvement as compared to the other group. Interestingly, the different cytokine background identifying SLE-SS patients, characterised by higher serum levels of TNFα, IL-6, MCP-4, MIP-1β, IL12/23 and IP-10, may the rationale for employment of targeted biologic therapy in this group of patients.

Subsequently, R. Gerli (Perugia, Italy) discussed about the intriguingly relationship between SS, autoimmune thyroid disease and coeliac disease. Indeed, a common genetic background and shared pathophysiological mechanisms may account for the high prevalence of autoimmune thyroid disease and antithyroid antibodies commonly detected in SS patients in comparison to other systemic autoimmune diseases. Moreover, based on a review of the literature and on the analysis of original data of a cohort of SS patients included in the large database of the Italian Research Group for SS (GRISS), it was demonstrated that SS patients with autoimmune thyroiditis are characterised by significant higher prevalence of coeliac disease in comparison to SS alone. Again, shared genetic background and analogue pathophysiological pathways may explain this association. The final part of the presentation was dedicated to the analysis of a large published Italian study which confirmed the striking higher prevalence of coeliac disease in a cohort of consecutive SS patients in comparison to general population and patients with other systemic autoimmune disease. Moreover, in this cohort, SS patients with coeliac disease had significant higher prevalence of autoimmune thyroiditis in comparison to non-coeliac SS patients. Better understanding of pathophysiological mechanisms underlying this association, of the role of gluten free diet in preventing long-term complications, as lymphoproliferative disease, and development of clear recommendations for screening of autoimmune thyroiditis and coeliac disease in SS represent current unmet needs to be investigated in future research.

Regarding the association between SS and systemic sclerosis (SSc), N. Del Papa (Milan, Italy) addressed important points. In particular, she highlighted that, although sicca symptoms are common in SSc patients, the real prevalence of associated SS in SSc is unknown due to the application of different classification criteria for SS. The true association between SSc and SS has been reported almost exclusively in the limited SSc and is characterised by a milder disease phenotype, with lower prevalence of lung fibrosis, pulmonary arterial hypertension and less immunosuppressive therapy need, and higher prevalence of anti-centromere antibody positivity. Interestingly, histologic analysis of SGB of patients with SSc and sicca symptoms demonstrated a fibrotic process mainly characterised by interstitial glandular fibrosis with normal and/or atrophic acini and without lymphocytic sialadenitis. Surely, clinical and pathophysiological profiles of patients with SS and concomitant SSc need to be further characterised.

On the other hand, the association between rheumatoid arthritis (RA) and SS is more frequent and G. Nocturne (Paris, France) made a critical literature analysis. Common genetic variations in TCR signalling pathway genes, shared signature/upregulated genes and common dysregulated immunologic mechanisms may explain such association. As far as clinical features are concerned, SS/RA patients are characterised by lower prevalence of parotid gland enlargement, higher frequency of articular and lung involvement, same risk of lymphoma and higher prevalence of rheumatoid factor and anti-cyclic citrullinated antibody positivity in comparison to SS alone. On the other hand, SS/RA patients display more systemic involvement (fever, rash, haematological abnormality), more active articular domain and higher frequency of rheumatoid factor. Moreover, patients with SS and RA may be characterised by a lower response to biological therapies.

The session was concluded by J. Anaya (Colombia) who focused on polyautoimmunity in SS. Latent and overt polyautoimmunity is frequent in SS and mainly characterised by the association with autoimmune thyroiditis, SLE, RA and SSc. Many factors have been identified that are associated with polyautoimmunity, including genetic background, gender (female), ancestry, familial autoimmunity and smoking. Interestingly, a recent large population-based study demonstrated that the risk of cardiovascular disease in patients with systemic and organ-specific autoimmune disease increased progressively with polyautoimmunity, being almost four times higher in patients with three or more autoimmune diseases in comparison to the general population (3). However, how polyautoimmunity affects major autoimmune diseases and the longitudinal effects of latent polyautoimmunity warrant further investigation.

Sixth plenary session

The nomenclature of SS

The sixth session was dedicated to the possibility of changing the nomenclature of SS. The session was introduced by A.G. Tzioufas (Athens, Greece) who provided an historical perspective of the nomenclature itself. A. Baer (Baltimore, USA) presented the International Consensus on Nomenclature and Classification for Sjögren aimed at developing a position paper for the nomenclature and classification of Sjögren's through international consensus following widespread scientific deliberation. The Convenors of the International Consensus were A. Baer (USA) and M. Ramos-Casals (Spain), whereas patient representatives were C. Bouillot (Europe) and K. Hammitt (USA). A. Baer illustrated the methodologic work and the Delphi process informed by bibliometric analyses and literature reviews underlying the International Consensus. He also extensively described the patient voice actively included in the consensus process. Regarding the Nomenclature issue, he summarised all the arguments against the "Sjögren's syndrome" and all the arguments in favour of "Sjögren's disease" and reported the results of the first Delphi round. 49% of the answers disagreed with maintaining the term "syndrome", 54% agreed or strongly agreed with changing to the term disease, 87% agreed or strongly agreed with maintaining the use of the eponym Sjögren, and 65% agreed or

strongly agreed that if the eponym was maintained, the usage of the non-possessive form Sjögren was recommended. P. Brito-Zeron (Spain) presented the classification issue regarding the Consensus about the use of the terms "primary", "secondary", "associated". Specifically, she presented the results of the first Delphi round. 46% of the answers agreed on maintaining the use of the term primary, 72% did not agree on maintaining the use of the term "secondary", 75% agreed, if the term "secondary" was not maintained, they recommended changing to the term "associated". She finally presented the results of a SLR that had analysed people with Sjögren coexisting with other ADs: the frequency of the overlap, the epidemiological profile, the frequency of SS antibodies, the frequency of active clinical ESSDAI domains and the problem of disease mimickers that can be associated with SS. She concluded with points to be discussed in the second Delphi round, regarding the exclusion from research studies of patients with coexisting systemic diseases or coexisting organ-specific diseases. Before the live discussion, K. Hammitt presented the patient view on the eponym. She showed that the majority of the patients agreed with maintaining the use of the eponym Sjögren, agreed to recommend the usage of the non-possessive form Sjögren and agreed with changing from "syndrome" to the term "disease". Regarding the classification issue, the vast majority of the patients did not agree to maintaining the use of the term "primary", did not agree to maintaining the use of the term "secondary" whereas they agreed with changing to the term "associated". The session was concluded by a round table with experts and plenary discussion.

Seventh plenary session

The involvement of different specialties in the care of SS

This session was dedicated to the analysis of unmet needs and importance of involvement of other specialists in the global management of patients with SS. Firstly, M. Jonsson (Bergen, Norway) made a general and complete update on news development in the management of dry mouth, particularly highlighting the importance of oral and dental hygiene with fluoride application and the regular use of local saliva substitutes. Moreover, a recent randomised, double-blind trial demonstrated the efficacy of ianalumab in overt time and dose-depending increase in unstimulated and stimulated salivary flow in SS (4).

The subsequent presentations were dedicated to the analysis of features specifically characterising paediatric SS. Firstly, S. Retamozo (Barcelona, Spain) reported original data driven by 158 SS patients diagnosed below 19 years of age and included in the Big Data Registry. Prevalence of childhood SS resulted 1.3% and mean age at diagnosis was 14±3.5 years. Glandular enlargement and dry mouth and dry eye were the most frequent manifestations at disease diagnosis, followed by fever, arthralgias, skin involvement and fatigue. Mean ESSDAI score at presentation was 7±6.7 and about 80% of patients had low-moderate disease activity with no high activity in any domain. Again, systemic phenotype was mainly dominated by glandular involvement, followed by lymphadenopathy and constitutional. Interestingly, no essential differences were detected between young-onset and childhood-onset patients except for higher prevalence of lymphadenopathy in young-onset and constitutional with anti-Ro antibody in 10–14 years patients. This suggests that the specific features seen in childhood-onset disease may reflect an early stage of SS. Then, A. Tomassini (Trieste, Italy) revised the importance of salivary gland ultrasonography and biopsy in the differential diagnosis of juvenile recurrent parotitis *versus* paediatric SS by the analysis of case reports.

The importance and influence of gender in disease phenotype is still a matter of debate and few studies have addressed this interesting topic. In her complete presentation, R. Priori (Rome, Italy) explored the role of epigenetic/genetic alterations and sex hormones in contributing to the striking higher prevalence of the disease in female sex. Moreover, different disease phenotypes characterise SS female and male patients. In particular, higher prevalence of sicca symptoms, Raynaud phenomenon, depression, fibromyalgia, and anti-Ro positivity identifies female SS patients while male patients display higher prevalence of pulmonary involvement, lymphoma risk, anti-La antibodies and a worse systemic phenotype. In the final part, problems related to impaired fertility, the impact of the disease on pregnancy (higher risk of premature delivery and low birth weight) and of pregnancy on SS, the risk of congenital heart block in anti-SSA positive women and breast-feeding were specifically addressed. Quality of sexual life in SS women represents a relevant problem due to vaginal dryness and dyspareunia. In this setting, a preliminary validation of a questionnaire (Qualisex) to assess the impact of the disease on sexuality in 40 sexually active SS women demonstrated a low quality of sexual life and mood disturbances, sicca symptoms, fatigue and pain, but not disease activity, contributed to worse score. On the other hand, endometriosis, pelvic floor dysfunctions, contraceptive methods, menopausal hormonal therapy and assisted reproduction technologies still represent open issues. Similarly, fatigue and chronic pain represent two important features of the disease, significantly impairing patient quality of life. P. Sarzi Puttini (Milan, Italy) highlighted the significant contribution of concomitant fibromyalgia in the perception of pain and fatigue in these patients, in particular in seronegative SS, being strictly related to the presence of fatigue and mood disorders, in particular depression. Mechanisms of pain and fatigue in SS, not completely understood, may likely involve multiple biological, physiological, psychosocial and behavioural pathways. Then, the need for a personalised and holistic approach to optimise the management of pain and fatigue in SS was highlighted. At the end of this session, E. Bartoloni (Perugia, Italy) and C. Baldini (Pisa, Italy) addressed the importance of referral pathways in specialised centres to improve disease management and outcome. In the first presentation, a specific referral pathway for SS was

proposed as the result of a large collaboration of several Italian specialists in order to improve early patient referral, to obtain early and correct disease diagnosis and for proper assessment of disease activity, prognosis, therapy and comorbidities. C. Baldini then presented the preliminary programme and activities of the European Reference Network (ERN-ReCONNECT), a collaborative networks of excellence including healthcare providers and patients' representatives aiming at improving quality, safety and access to highly specialised healthcare and promoting the interaction between patients and clinicians of different specialities at European level. In particular, a six-phase new methodology (RARERN-PATH) designed for the development of common and shared organisational reference model for patients' pathways in rare and complex diseases, including SS, was presented.

Eighth plenary session

pSS and COVID-19 infection

The eighth plenary session was dedicated to COVID-19 infection. The theme was introduced by M. Galli (Milan, Italy) that provided an extensive overview on the liaison between autoimmunity and COVID-19. Indeed, patients with systemic autoimmune diseases have an increased risk of a worse evolution of COVID-19. The key factors that modify the COVID-19 prognosis include the epidemiological profile, comorbidities and underlying therapies. Following this introduction, P. Brito-Zeron (Barcelona, Spain) specifically focused on COVID-19 in SS patients. She explained why COVID-19 might be relevant for SS patients highlighting the mucosal impairment that might facilitate SARS CoV-2 infection; the cardiovascular burden that might influence COVID-19 prognosis; the fact that some systemic features (ILD, lymphomas) may worsen SARS-CoV-2 infection and that patients under treatment with glucocorticoids, immunosuppressants or rituximab may have poor outcomes. She presented data on the first wave and on post-COVID-19 syndrome. The COVID-19 first wave produced increased number of adverse outcomes among older people, with higher hospitalisation rates in SS patients with comorbidities, respiratory symptoms, pneumonia and lymphopenia. Post-COVID-19 syndrome was described in 29% of the patients frequently reporting hair loss, red eyes, neurological symptoms and musculoskeletal symptoms. Finally, she presented data on SARS-CoV-2 vaccination. The literature data showed that COVID-19 vaccination was safe in SS patients with similar rates of side effects than that observed in non-autoimmune subjects. The rate of systemic disease triggered by COVID-19 vaccination was 1.2% with all cases completely recovering after being manged with symptomatic or corticosteroid therapy.

Ninth plenary session

Evolving topics in pSS therapy

The ninth session focused on pSS therapy. M. Ramos-Casals (Barcelona, Spain) illustrated the recent EULAR recommendations for the management of SS starting from glandular symptoms. He specifically mentioned some of the current unmet need in sicca management including the absence of an effective cure for glandular dysfunction and the difficulties in RCT design for sicca symptoms control. Regarding systemic diseases, he highlighted the need for multidisciplinary, multidimension approach to chronic pain and fatigue, the lack of solid evidence about how to use glucocorticoids, immunosuppressive drugs and biologics, as well as the lack of solid evidence about organ-specific therapeutic approach. He concluded that SS should be considered a true orphan disease from a therapeutic point of view, with the absence of intervention curing the disease.

S. Bowman (Birmingham, UK) discussed possible inputs derived from SS recent clinical trials by providing an extensive overview on the most relevant clinical trials of DMARDs in pSS. He highlighted the importance of novel composite measures characterised by a higher sensitivity to change (*i.e.* CRESS; STAR) and pinpointed the complexity of the possible therapeutic targets considering the disease pathogenesis. Finally, he mentioned possible further endpoints to be evaluated in RCTDs including SGUS and histology. S. Arends (Groningen, The Netherlands) expanded the concept of patient selection and composite endpoints. Particularly, regarding patient inclusion, she suggested the combination of inclusion criteria whereas she underpinned the concept that composite endpoint may capture multiple clinically relevant aspects of pSS. Finally, G. Illei (USA) provided the industry perspective regarding novel therapies development for SS. He firstly illustrated the drug discovery process and then analysed some of the determinants of the process itself including the biologic plausibility, the unmet need, the clinical development feasibility, the regulatory feasibility, the drug supply and the commercial feasibility, all crucial aspects that influence the company strategies. Regarding SS specifically, he recognised the clear change in interest in SS from industry with 21 interventional active trials listed in clinicaltrials.gov, but also the challenges in defining unmet need in SS drug development.

Tenth plenary session

Evolving topics in health policies

This session was dedicated to health policies and patient needs. In the first part of the session C. Seghieri (Pisa, Italy) and J. Barrio Cortés (Madrid, Spain) shared their experience gained within the HarmonicSS project regarding geographical variation in pSS diagnosis and management across Europe. C. Seghieri presented the results of two surveys mapping the patient experience on pSS diagnosis and long-term management across Europe. In 240 newly diagnosed SS patients, she reported an average time to diagnosis of 6.47 years and an average number of diagnostic tests per patient of 3.59. Number and determinants of volume visits and exams were also examined in 395 patients showing significant variations among countries. Barrio Cortés reported the results of a population-based cross-sectional study SS patients with a diagnosis confirmed by a physician from Madrid Public Health Rare Dis-

eases database (SIERMA). The study offered the perspective of the general practitioner, not only in terms of disease prevalence but also of comorbidities and real-life therapies.

In the second part, A. Vieira (EULAR PARE) and K. Hammitt (San Francisco, USA) reported the patients' voice and advocated for greater patient involvement and participation in research and any other relevant area in order to identify and help to address the numerous unmet needs, thus promoting the advancement of knowledge, research, information, treatment and care in SS.

Eleventh plenary session

Evolving topics in cooperative research

This final session was aimed at providing a general overview of the existing collaborative research in Europe. V.C. Romao (Lisbon, Portugal) presented ERN ReConnet, the European Reference Network on connective tissue and musculoskeletal diseases aimed at improving quality, safety and access to highly specialised healthcare. C.H. Shiboski (San Francisco, USA) presented a new multi-centre US SS Disease Research collaboration: Sjögren's team for accelerating Medicines Partnership (STAMP) that aims to initiate the deconstruction-reconstruction of SS through the analysis of the molecular and clinical data. M. Ramos-Casals (Barcelona, Spain) presented the Sjögren Big Data Consortium, an international, multicentre registry designed in 2014 to take a real-world picture of the phenotypes and outcomes of people with pSS. J.-O. Pers (Brest, France) presented the PRECISESADS study, a collaborative EU project that aims to further study biomarker characterisation combined across existing disease boundaries to reveal new insights. A.G. Goules (Athens, Greece) presented the post-HarmonicSS era with the project PRECIOUS to foster the creation of a high-performance cloud computing infrastructure specifically oriented towards lymphomagenesis prediction. R. Seror (Paris, France) provided an update of the Necessity project particularly regarding the novel clinical endpoint (STAR), the Necessity clinical trial design that is ongoing. Athanasios Tzioufas (Athens, Greece) provided an updated on the projects ongoing within the eSSential - EULAR Sjögren's Syndrome Experimental and Translational Investigative Alliance Study Group that focuses on experimental and translational research in SS. He particularly mentioned the PreSStige study that aims to characterise the early stages of the disease. Finally, C.J. Lessard (Oklahoma City, USA) presented an update of the Sjögren's genetic Network (SGENE) illustrating the current status of the SS GWAS project. This was the last session before the closing remarks and the poster awards. The 16th International Symposium on Sjögren's syndrome will be held in Egmond aan Zee, The Netherlands, in Spring 2014.

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