fatigue, depression and the social impact of the disease, and (4) Being involved – individually and collectively.

Methods LUPUS EUROPE is the umbrella organisation that federates, since more than 30 years, national self-help lupus groups around Europe. Through a wide range of initiatives, it seeks to bring alive its vision of ‘a better life for people with lupus in Europe, until we reach a world without lupus’.

Results Lupus Europe actively works on all drivers of a better life with lupus. This is constant work in progress with multi-party collaboration

- a. Prompt diagnosis – Awareness events are run locally, but more must be done, particularly for GP’s, ensuring that lupus signals are identified and testing/referral to expert is done much earlier.
- b. Access – Only 54.3% of European patients are satisfied about their lupus care. Patients expect much awaited new treatments, with a focus on corticoid reduction and targeted therapies for those not responding to standards of care. Lupus Europe engages with academics and industry in more than 20 projects to better understand the disease and design better treatments; and with ERN-ReCONNET to bring best available care to all in Europe. The Patient Advisory Network is available to support your projects with significant patient’s added value.
- c. Fatigue, depression and social impact: treating lupus is one thing, but even when lupus is controlled, a significant proportion of patients continue to claim debilitating fatigue, depression, or the inability to participate fully in a social life. Much remains to be understood and resolved. Lupus Europe will conduct a survey ‘living with lupus in 2020’ to measure evolution since our 2010 survey. In the meantime, we are not powerless: (i) Lupus Europe designed an exercise program, endorsed by the ERN to help patients start fight fatigue with exercise, regardless of their current fitness level, and (ii) practical tips based on social psychology and patient experience can help fight depression.
- d. Being involved – Individually: Our patient panel on adherence highlighted that being involved in the decision making (feeling listened to, understanding the disease/treatment, and shifting from ‘YOUR prescriptions to OUR treatment plan’) is key to increase adherence.
- e. Being involved – Collectively: Patients are increasingly ready to be involved in the fight against lupus and to be trained to help. ‘Nothing about us without us’ is not a political motto, but a strong desire to be part of the solution. Our experience shows that involving patients in research is a triple win: win for the project, (funding or process often requires patient involvement), win for the team (new insights and out of the box thinking from collaborating patients), and win for the patient (being involved has a therapeutic effect and hopefully results in a better end product/treatment). Many patients do not know how they can be involved in research close to their homes. When options are explained by a person they trust (#1 is their rheumatologist), a majority is interested in taking part. A key area of work to concentrate on is to train both patients and researchers so that patient involvement is not perceived as an additional burden in an already very full schedule, but a valuable help, even very early in the process.

Interestingly, interactions with patients repeatedly highlight the precious link established between patients and their lupus specialist. Patients are incredibly thankful to their doctors for their commitment, knowledge and relentless efforts to support

them, so often way beyond professional obligations. One can say that one of the patient expectations is also to have a ‘happy rheumatologist’, and there also, we are willing to help.

Conclusions Unsurprisingly, Patient’s expectations are to have ‘A better life’. Working together, much progress has already been made, and LUPUS EUROPE is committed to keep working on this, together with all partners.

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18 THE ROLE OF THE INTERFERON SYSTEM IN SLE

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The interferon (IFN) system can be defined as the IFN genes and proteins, the inducers of IFN production, the IFN producing cells, as well as target cells affected by IFN. There are three different types of IFN (I–III), and type I IFN is the largest family consisting of more than 15 different proteins. The type I IFNs are our main defense against viral infections and production can be triggered by ligation of several different sensors of nucleic acid. Most cells can produce small amounts of type I IFN, but the principal type I IFN-producing cell is the plasmacytoid dendritic cell (pDC).

There are several observations suggesting an important role for the IFN system in the etiopathogenesis of SLE, but also other autoimmune diseases. Among these are the reported development of SLE during treatment with IFN- α , a prominent increase in the expression of IFN regulated genes (an IFN signature) in SLE, the existence of endogenous, or self derived, IFN inducers in SLE patients and a genetic association between SLE and gene variants within the type I IFN signaling pathway.

Several studies have shown that type I IFN seems to be the most important IFN for inducing the IFN signature, but it’s clear that type II and type III IFNs also can contribute. Furthermore, patients with SLE have epigenetic changes in type I IFN regulated genes, which are hypomethylated. Thus, there are strong evidences that activation of the IFN system, and particular the type I IFNs, is a key event in the SLE disease process.

The type I IFN system is closely connected to a number of other cytokine and chemokine pathways, which all can contribute to both the IFN signature and type I IFN effects. Important type I IFN effects are maturation and differentiation of dendritic cells, activation of T and B cells with enhanced antibody production and induction of increased expression of autoantigens. Consequently, type I IFNs can act as an immune adjuvant and promote an autoimmune process. Furthermore, the regulation of the type I IFN system is abnormal in SLE and negative feedback mechanisms are impaired, causing a positive feed-forward loop, which sustain the autoimmune reaction. Many different therapeutic targets exist within the IFN system and several studies have recently been published showing beneficial effects of blocking or down-regulating the activated type I IFN system in SLE. However, not all patients with SLE improve during IFN inhibition and obviously; better stratification of patients and more precise treatments are needed in the heterogeneous group of SLE

patients. This can be done by integrating clinical phenotype with genetic setup, gene expression profile and analysis of activated pro inflammatory pathways.

19 CLINICAL TRIALS WITH IFN BLOCKERS

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Background Type I interferon (IFN) pathway activation has long been demonstrated in patients with systemic lupus erythematosus (SLE). The target of drug development in SLE, approaches to inhibit type I IFN have been quite eclectic. The initial strategy, which utilized a monoclonal antibody to interferon-alpha, was not successful as the phase 2 study in SLE with rontalizumab failed to achieve the primary end point of the study. Shortly thereafter, the results of a phase 2 SLE study with sifalimumab, a second monoclonal antibody to interferon-alpha, were released. While benefit was achieved, the pharmacodynamic and clinical effects were not as robust as those attained in a phase 2 SLE study with anifrolumab, an antibody to the type I IFN receptor that inhibits all type I IFNs. The phase 3 anifrolumab program was comprised of two studies, known as TULIP 1 and TULIP 2. TULIP 1 evaluated two doses (150 and 300 mg) administered intravenously every 4 weeks through week 48 with the primary end point, SLE Responder Index response rate, at week 52. Although this study failed to achieve the primary end point, it was recognized after unblinding that 8% of study subjects were misclassified as non-responders because of NSAID use. While post-hoc revisions to the restricted medication rules did not change the primary outcome of TULIP 1, these modifications did result in several successful secondary outcomes, including the British Isles Lupus Assessment Group-based Composite Lupus Assessment response rates (BICLA: placebo [29.6%] vs anifrolumab 300 mg [46.1%]). An additional outcome of the post-hoc evaluation of TULIP 1 was the modification to the TULIP 2 primary end point.

TULIP 2's initial design was identical to TULIP 1 with the exception that just one dose of anifrolumab (300 mg) was compared to placebo. However, before unblinding, the end point was switched from SRI at week 52 to BICLA response rate at week 52. TULIP 2 not only achieved the primary outcome (BICLA: placebo [31.5%] vs anifrolumab 300 mg [47.8%]), but multiple secondary end points were also attained, chief of which were the ability to taper corticosteroids as well as improvement of cutaneous disease activity. Safety signals of note included a higher rate of herpes zoster reactivation (placebo: 1.1% vs anifrolumab: 7.2%).

While not as advanced in development, there are several other programs that are targeting the IFN pathway. RSLV-132 is an RNase-Fc fusion protein that enzymatically degrades circulating RNA, thus inhibiting its ability to bind to toll-like receptors (TLR) and activate plasmacytoid dendritic cells. Direct inhibition of TLRs is yet another strategy being employed to target the innate immune system. Immunization with an IFN-alpha-KLH conjugate allows the host to produce his or her own antibodies to IFN-alpha. Plasmacytoid dendritic cells (pDC) are the major producers of type I IFN, and thus they represent a principal target for SLE drug development. BIIB059 is a monoclonal antibody that binds BDCA2, a

protein uniquely expressed on pDCs. When BDCA2 is ligated with BIIB059, the protein is internalized, and production of cytokines, chemokines, and interferons is inhibited. In late 2019, it was announced that two phase 2 studies that evaluated cutaneous lupus as well as SLE achieved their respective end points. Baricitinib, an inhibitor of JAK1 and JAK2, achieved success in a phase 2 SLE study and is currently in phase 3. Let's not forget hydroxychloroquine, which suppresses TLR activation through its inhibition of endosomal acidification.

The future is bright for patients with SLE as research is providing greater insights into SLE pathogenesis that are being translated to drug discovery.

110 CARDIOVASCULAR DISEASE BURDEN AND BIOMARKERS IN SLE

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Background Premature vascular disease is a major clinical problem and the major cause of the shortened life expectancy observed among patients with SLE in modern societies. Both ischemic heart disease (IHD) and ischemic cerebrovascular disease (ICVD), is common in SLE, 10% and 12% respectively in our cross-sectional Swedish study. The risk estimates for VD in SLE are comparable to diabetes and premenopausal women are at particularly high relative risk. Only a minor part of the vascular risk in SLE is explained by abundance of traditional cardiovascular risk factors. Thus, the major reasons for SLE related VD is associated with autoimmunity and SLE per se.

Methods This presentation will review current literature with focus on confirmed and recent findings which can explain why patients with SLE are so commonly affected by VD. Special focus will be given to biomarkers which are associated with the occurrence of VD, and which can serve to select patients in need of preventive treatment.

Results The focus of this presentation will be on SLE related vascular risk factors, but also on vascular outcomes and the temporal relationship between disease onset and VD.

Risk factors seem to differ between various hard vascular outcomes e.g. myocardial infarction, stroke and venous thromboembolism. Many studies use subclinical atherosclerosis or other measures of vascular vulnerability as outcomes, these are important to study but they should be distinctly separated from hard vascular events.

The following patient subgroups/biomarkers will be discussed in the context of SLE related VD: 1) Nephritis and impaired renal function, 2) Antiphospholipid antibodies 3) Complement activation, 4) Systemic inflammation 5) Genetic predisposition. In the clinic there is an interaction between all these factors and also traditional cardiovascular risk factors, which result in high risk for VD. Another approach is to subgroup SLE patients depending on autoantibodies and thus identify subgroups of patients with high risk for VD.

Conclusions Through early mapping and recognition of vascular risk factors in patients with SLE, it should in the future be possible to tailor preventive treatments to individual patients. The goal is to reduce and eventually prevent the heavy burden of vascular disease among patients with SLE.