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The mosaic of autoimmunity – Finally discussing in person. The 13th international congress on autoimmunity 2022 (AUTO13) Athens

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ABSTRACT

While autoimmunity is a branch of medicine linked to every single organ system via direct and indirect pathways, meeting in person to discuss autoimmunity during the 13th international congress on autoimmunity (AUTO13) with participants from all over the world had a very good reason. The mechanisms involved in autoimmune diseases are of extreme importance and in fact critical in understanding the course of diseases as well as selecting proper therapies. COVID-19 has served as a great example of how autoimmunity is deeply involved in the disease and directly correlated to severity, morbidity, and mortality. For instance, initially the term cytokine storm dominated, then COVID-19 was addressed as the new member of the hyperferritinemic syndrome, and also the use of immunosuppressants in patients with COVID-19 throughout the pandemic, all shed light on the fundamental role of autoimmunity. Unsurprisingly, SARS-CoV-2 was called the "autoimmune virus" during AUTO13. Subsequently, the correlation between autoimmunity and COVID-19 vaccines and post-COVID, all were discussed from different autoimmune aspects during the congress. In addition, updates on the mechanisms of diseases, autoantibodies, novel diagnostics and therapies in regard to autoimmune diseases such as antiphospholipid syndrome, systemic lupus erythematosus, systemic sclerosis and others, were discussed in dedicated sessions. Due to the magnificence of the topics discussed, we aimed to bring in our article hereby, the pearls of AUTO13 in terms of updates, new aspects of autoimmunity, and interesting findings. While more than 500 abstract were presented, concluding all the topics was not in reach, hence major findings were summarized.

1. Introduction

At the time the restrictions imposed by the pandemic of COVID-19 started to ease, one could not wish for a better reason to travel to Athens to attend the 13th international congress on autoimmunity 2022 (AUTO13). In addition to the importance of autoimmunity, the event itself, was a piece of art in all of its components, starting from the city, venue, attendees, presenters, and the topics discussed [1]. In fact, autoimmunity as the center and main motivator for the gathering for the 13th time, deserves all of the attention given, and rightly so. The importance of autoimmune mechanisms and diseases, in almost every domain in medicine cannot be overemphasized. For instance, autoimmunity has been linked to all body systems, almost with no exception [2–4]. Moreover, early in the pandemic of COVID-19, the association of COVID-19 with autoimmunity has been thoroughly reported in the medical literature [5,6]. Unsurprisingly, the latter topic had an extensive attention during AUTO13 due to its significance and relevance while the world is still coping with the pandemic. Vaccines in general, and those against COVID-19 in particular, had dedicated sessions during AUTO13 as well. Actually, while vaccines have long been associated with autoimmune side effects and disorders [7,8], COVID-19 vaccines were shown to be related with autoimmune manifestations and diseases [9]. Therefore, based on the domains mentioned and searched, more than 500 abstracts were accepted to AUTO13, divided into both oral and poster presentations. The plenary sessions of AUTO13 specifically, included high-standard lectures presented by leading researchers. Among others, latest updates on the mechanisms of autoimmune diseases, novel diagnostics and therapies were illustrated. Due to the greatest value of the international congress on autoimmunity, such as AUTO13, primarily because of its contents, and secondarily as it was held in person after a period of virtual meetings during the pandemic of COVID-19, we found it of extreme importance to conclude the topics, discussions, and the pearls gathered during the AUTO13 and bring them hereby in our paper. The summary of the studies discussed is critical in our opinion, to the present and future research in the field of autoimmunity. Nevertheless, as hundreds of abstracts and presentations could not be concluded in one article, we summarized the most leading, innovating, and updated topics presented during AUTO13.

2. Virtual versus in person

We are full of appreciation and respect for the community of researchers and those dealing with the improvement of understanding diseases, as well as providing diagnostic and treatment options, for the fact that medical congresses continued to be held virtually during the pandemic of COVID-19. Our colleague Jan Damoiseaux addressed the special features and characteristics of virtual meetings in our article summarizing the 12th international congress on autoimmunity 2021

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(AUTO12) held virtual [4]. Among others, of the advantages mentioned by Damoiseaux were the unique ability to choose which sessions and presentations to attend at the push of a button, as there is no need to walk and move fast between halls to catch presentations on time. Furthermore, while talks were prerecorded, time prolongation and violation, if to say, rarely occur during virtual meetings. The privilege of stopping and repeating the records when needed for better listening or looking at a slide, are of great value as well. Having said that, in person meetings, still possess their shine alongside numerous advantages. Face-to-face meetings, in autoimmunity for instance, serve as a base for establishing cooperation in such a thirsty field for research and development. Meeting in person, have certainly contributed to an upgraded experience, where students and young doctors met leading professors, diagnosticians helped treating physicians, and most importantly asking questions and allowing discourse and discussions. While virtual gatherings kept the tradition of knowledge sharing viable, it is challenging to find a replacement for in person meetings, without a doubt.

3. Art was also a part of AUTO13

In a nice gesture to art in medicine, Cohen Tervaert illustrated beautifully how diseases were depicted in art throughout history. The author showed portraits, painted by famous artists such as Frans Hals, of people with Heberden nodules long before being described in the medical literature [10]. The presenter emphasized the importance of observing in medicine and how art contributed to sharpening the skills of physicians and improved diagnosis [11].

4. Basic components of autoimmunity during AUTO13

4.1. Mechanisms

Revealing the underlying mechanisms inducing autoimmune response carries great importance to develop more efficient and targeted therapies for autoimmune diseases. Moreover, a great number of studies investigated the mechanisms triggering various proteins in the body to become autoantigens. Biedermann investigated the possible self-antigenic potential of topoisomerase 1 (TOP1) cleavage complexes (Top1cc) which are protein–DNA cleavage complexes linking TOP1 to DNA strand breaks [12]. Biedermann hypothesized that Top1cc could function as self-antigen and triggers autoreactive B-cells bypassing T cell dependency. For this reason, the author aimed to test whether the increased number of Top1cc could contribute to an autoimmune disease. In order to impair the repair of ribonucleotides and to increase Top1cc which stabilizes the nucleosomal breaks, a knockout of the RNaseH2 genes in vitro was conducted. However, knock-out cells could not demonstrate an increase in Top1cc despite a successful defect in RNase H2 [13]. Some of the mechanisms responsible for evoking autoimmune responses are closely related to the functioning of the immune system. Rikhi and friends examined the dominancy and phenotype of T cell subsets in 8 patients with immunodeficiency of Wiskott-Aldrich syndrome (WAS) [14], as patients with WAS were found to be prone to developing autoimmune manifestations [15]. Among the 8 patients studied, 4 developed an autoimmune disease. The flow cytometry analysis revealed an imbalance in the Th1/Th2 ratio favoring Th2 dominancy in all 8 patients. On the other hand, the authors found a decrease in follicular T helper (TFH) cells in only 4 patients with WAS who developed autoimmunity, which was not the case in WAS patients without autoimmunity neither in healthy controls. Further investigation of T cell subsets and phenotype dominancy could shed light on the unknown mechanism of autoimmune phenomena in WAS, the authors concluded. Furthermore, a study on immune system components and their roles in autoimmunity was conducted by Achour and colleagues. It is known that TFH induce B cells to terminally differentiate into antibody-secreting plasma cells [16]. Achour et al previously demonstrated that regulatory B (Breg) cells inhibit TFH-induced plasma cell activation and resulting antibody secretion [17]. In their recent study, the group aimed to test whether modulating Breg cells have an effect on TFH cell-mediated antibody secretion in the settings of autoimmune diseases such as primary Sjogren's syndrome and SLE. In vitro differentiation of human T cells into TFH cells was performed. Furthermore, co-culture of resulting TFH cells and B cells derived from Sjogren's syndrome and SLE patients lead to plasma cell differentiation and IgM, IgG, and IgA secretion. When Breg cells were added to TFH-B cells co-culture derived from healthy patients and Sjogren's syndrome, they dampened the plasma cell differentiation and antibody production. However, Breg cells did not inhibit TFH-mediated plasma cell and antibody formation in co-cultures derived from SLE. The authors concluded that an impairment in Breg cells may be responsible for TFH-dependent humoral response in SLE. Similar findings were reported before, strengthening the conclusion of the authors [18–20]. Last but not least, stress has long been believed to play a critical role in initiation and exacerbation of the autoimmune disorders [21]. Katz and friends revealed a higher prevalence of the autoimmune diseases among survivors of the Holocaust in Israel possibly linked to horror and extreme stress experienced at that time. In their study, 105,995 Holocaust survivors were matched to 105,995 controls. The analysis showed that the prevalence rate of autoimmune disease was 87 per 1,000 (0.087) in the study group. Among autoimmune diseases, psoriasis was the most prevalent autoimmune disease in both groups and its prevalence was higher in Holocaust survivors (0.046) compared to the control group (0.014). Similar findings were reported previously [22,23].

4.2. Autoantibodies

Developing more sensitive, specific, and convenient detection methods for autoantibodies is extremely important for the diagnosis and prognosis of autoimmune diseases. In the session concerning autoantibodies, a great number of researchers introduced their studies on developing novel autoantibody detection systems and standardization methods [24]. For instance, Keppeke and friends proposed a new cell-based assay (CBA) for the detection of anti-fibrillarin autoantibodies which are used in the diagnosis and prognosis of Systemic Sclerosis (SSc). It is known that presence of anti-fibrillarin antibodies could be determined based on their characteristic clumpy nucleolar pattern on HEp-2 cells in indirect immunofluorescence assay. In clinical practice, immunoprecipitation and solid-phase immunoassays (SPIA) are the methods for detecting anti-fibrillarin antibodies. However, both methods have their own drawbacks. While the gold standard for detecting the anti-fibrillarin antibodies is immunoprecipitation (IP); it requires expertise besides the need of radioactive materials which hinder its applicability in routine use [25]. The authors suggested a novel strategy of relocating the fibrillarin antibodies to the membrane and compared the performance of the newly developed assay with IP and other commercial solid-phase immunoassays (SPIA) such as line-blot and ELISA in the study. HEp-2-IFA detected a total of 62 samples with high-titer nucleolar patterns. Of the 62 samples, 21 with a homogeneous pattern, and 41 in a clumpy pattern. The 62 samples were tested in the fibrillarin- CBA, immunoprecipitation, line-blot and ELISA. In regard to the CBA results, 38 of 41 clumpy nucleolar samples (92.7%) were tested positive for anti-fibrillarin, and all 21 homogeneous samples were negative, consistent with HEp-2-IFA. The authors concluded that the new detection method was superior to other SPIAs and as sensitive and specific as IP. Another cell-based assay to detect antibodies which are used for diagnosis of neuroimmune diseases more effectively have been developed by another group, Karagiorgou and colleagues. Neuronal nicotinic acetylcholine receptors (nAChRs) which are highly expressed in the central and peripheral nervous systems were shown to be linked to autoimmunity [26]. Conventionally, the detection of α3-nAChRs antibodies with a radioimmunoprecipitation assay (RIPA) is used for the diagnosis of autoimmune autonomic ganglionopathy (AAG) [27]. However, several reports demonstrated that low levels of α3-

nAChR antibodies were reported in other neurological diseases as well [28]. These findings motivated the group to come up with a more specific detection method for the potentially pathogenic nAChRs antibodies found only in AAG. The authors developed a live cell-based assay (CBA) by using alpha3-nAChR transfected cells and compared CBA and RIPA which was previously established. The cohort included patients with suspected and/or diagnosed with autonomic failure whereas the controls had other neuroimmune diseases. At the end of the experiments, 25 patients tested positive for alpha3-nAChR antibodies by RIPA while CBA detected positive only in 15 out of the 25 patients. Most importantly, the study revealed that all CBA-positive patients were suffering from AAG while CBA-negative patients had other neuroimmune diseases. The authors showed that in comparison with RIPA, the specificity of CBA is higher, and the sensitivity is at least equal [29].

In addition, Hoovels et al evaluated different commercial assays used to detect rheumatoid factor (RF) and anti–citrullinated protein antibodies (ACPA) to achieve an interpretation standardization. Eighteen different assays from 13 different companies for RF and ACPA (9 for each) were tested on 398 samples from rheumatoid arthritis (RA) patients and 1073 healthy controls. The results showed that the sensitivity and specificity varied significantly between assays. According to the report, the interval-specific likelihood ratio (LR) of the test results was consistent across the various RF and ACPA assays. ACPA tests showed higher LRs than RF and %22 RA patients reported to have ACPA levels with LRs more than 80. Revisiting antibody level thresholds and determining test result interval-specific LRs could allow better adjustment of ACPA and RF assays to clinical practice, the authors concluded [30]. Furthermore, during the autoantibodies session, Mahler hypothesized that autoantibodies do not only aid in diagnosis of autoimmune diseases, rather they may also be useful in classifying patients into disease subgroups [31]. Mahler claimed that despite the huge advances in science, there is still a gap between new findings of basic science and clinical practice [32,33]. The author speculated that harnessing the autoantibodies in the stratification of patients could lead not only to more personalized and efficient treatments but also to predicting the disease [34,35]. New aspects of autoantibodies in Celiac disease was addressed by Lerner. The most common autoimmune diseases related with Celiac Disease (CD) are autoimmune thyroiditis and diabetes mellitus type 1. Several immunogenetic theories like epitope spreading, sharing common HLA genes and antigenic mimicry explained the presence of antibodies against many tissues and organs, including but not limited to endocrine pancreas, smooth muscle, liver, anti-gastric, collagens and bone in patients with Celiac disease [36].

4.3. Cytokines

The cytokine storm seen in COVID-19 and its effects on the immune neuroendocrine system by Jara and colleagues started the discussion of this important session. As a result of the multi-organ involvement found during the acute and post COVID-19 phases, high-risk patients (>65 years old, with comorbidities) may experience cytokine storms during the course of COVID-19. It has been shown that SARS-CoV-2 infection can alter the immunological neuroendocrine system both during the invasion stage of various organs and tissues and during the recovery stage. The combination of viral infection alongside the cytokine storm are to blame for this harm. The main stress response systems are: 1. hypothalamic-pituitary-adrenal (HPA) axis, 2. hypothalamic-pituitary-thyroid (HPT) axis, 3. hypothalamic-pituitary-gonadal (HPG) axis, 4. prolactin/growth hormone System, and 5. autonomic Nervous System. The interaction between immunity and neuroendocrine is activated by stressors such as infectious diseases, autoimmune diseases, and trauma. The presentation discussed the devastating effects of SARS-CoV-2 infection and cytokine storm on the immune neuroendocrine system [37].

The role of macrophage migration family of cytokines in autoimmune disease was presented by Nicoletti. The Macrophage Migration Inhibitory Factor (MIF) is a cytokine that plays a part in the development of a number of immune-inflammatory diseases. MIF binds to the intracellular receptor JAB1, the cell-surface receptor CD74, and the non-cognate receptors CXCR2 and CXCR4. Due to the significant functions of MIF in both innate and acquired immune responses, the responsibilities of MIF in the regulation of immunologic response are varied. Caltabiano et al supported the suggestion that MIF plays an important key factor in autoimmune diseases [38].

Sciascia discussed the interesting and complex interaction between SLE and APS and the involvement of cytokines. Early and late signaling processes that occur as a result of the abnormal T cell response to antigen lead to an unbalanced production of cytokines, such as reduced IL-2 and elevated IL-17. IL-17-producing T cells also have greater capacity to infiltrate tissues and support the inflammatory response. IL-23 is essential for the development of several autoimmune disorders. Autoimmune illness is inevitably developed in humans and animals missing IL-2 or FoXP3 which regulate the formation of Treg cells. It is currently widely employed as a new strategy for treating autoimmune disorders, where IL-2 is the first-in-class cytokine, to restore immunological tolerance by increasing and activating Treg cells. Larger studies are required to determine how IL-2 might complement the present treatment landscape in reducing a pro-inflammatory state, for example, from immunosuppressive drug combinations in very active inflammation to monotherapy in moderate illness. This has been discussed before which in fact strengthens the talk of Sciascia [39].

A study about serum cytokines as a biomarker of primary biliary cholangitis was conducted by Bauer and friends. The study included 192 patients and 50 controls. Due to their pro-inflammatory activities, cytokines IL-8, IL-17, and TNF- α may have a significant role in liver disease, particularly in the progression of the inflammatory process. The authors concluded that serum cytokine measurements can be employed as indicators of the severity of illness. Actually, cytokines such as IL-8, IL-17, and TNF- α have been shown to serve as biomarkers alongside variuos implications in other diseases [40–42].

Therapeutic aspects and opportunities for vitiligo were discussed by Khaitan. The melanocytes, which are mostly found in the skin and mucosae, affected by vitiligo, an acquired chronic pigmentary condition characterized by autoimmune destruction of melanocytes. Vitiligo is a psychologically taxing and visually debilitating disorder. The quality of life has been further lowered by its autoimmune character, which leads to chronicity, inconsistent responses to therapy modalities, and recurrent recurrences. Therefore, the goal of treatment should focus on prolonging remission time, preventing recurrences, providing pleasing aesthetic results, and assuring patient satisfaction [43]. The primary methods to largely accomplish the specified objectives are promoting melanogenesis and inhibiting cytokine signaling through targeted immunotherapy using corticosteroids and other immunosuppressants. Immunosuppressants are primarily used to stop the course of the illness, and they also cause re-pigmentation, possibly by enabling the preexisting melanocytes to function more effectively in an environment with less autoimmunity. The safer oral corticosteroid micro pulse (OMP) therapy has largely taken the role of daily corticosteroids in the treatment of vitiligo. OMP has been used with various therapeutic modalities, including phototherapy, photochemotherapy, and immunosuppressants, notably azathioprine and cyclophosphamide.

4.4. Complements

The complement system is an essential component of the innate and adaptive responses of the immune system, and it plays a vital role in fighting infections [44]. The levels of C3 and C4 have been strongly linked to the diagnosis of SLE, however, the levels are not reliable as in some cases they might be misinterpreted [45]. A newly developed research indicating that the split products of the complement system may be useful in the diagnosis and tracking of disease activity in SLE patients was presented by Weinstein [46]. In addition, Weinstein and

colleagues worked on the efficiency on the use of a multianalyte assay panel (MAP) in the diagnosis of SLE. They performed a retrospective study on 161 patients in 12 different centers in the USA, the investigators reviewed records at three different time stamps 1. (T0) when the MAP was ordered, 2. (T1) when the results of the MAP were reviewed by the physician, 3. (T2) any medical record that was at least 8 months after T1. The investigators analyzed the confidence of the SLE diagnosis and found that the confidence in the diagnosis increased by 1.74 times for every unit of increase in the MAP score, on the other hand, the confidence in the SLE diagnosis was low and very low in 35% and 49% of patients with negative MAP scores, respectively. Moreover, more patients were initiated with hydroxychloroquine (HCQ) following a positive MAP test compared to patients with a negative MAP test [47]. The role the complement system plays in the pathophysiology of APS was illustrated by Philip et al during the session on complement. The presenter also addressed the autoantibodies against the complement system found in patients with APS patients. Of the autoantibodies mentioned, anti-C1q autoantibodies were found to possibly contribute to the activation of the complement pathway [48]. Furthermore, as APS is associated with pregnancy complications [49], some studies suggest that activation of the complement system may be the cause of pregnancy complications in aPL antibodies carriers [50]. Based on that, Lini and colleagues studied the effect of hydroxychloroquine (HCQ) administration in aPL pregnant carriers and APS pregnant women. The results showed that treatment with HCQ on top of the traditional treatment of low dose aspiring (LDA) and low molecular weight heparin (LMWH) in women with triple aPL positivity and compliment consumption had significantly better pregnancy outcome compared to patients taking LDA and LMWH without HCQ [51]. In terms of therapeutic implications, the use of complement pathway inhibitors, specifically targeting the C5a receptor pathway, in the treatment of ANCA-associated vasculitis (AAV) was presented by Tervaert. The therapy suggested was shown to lead to better outcomes in patients with AAV. The findings were supported by several studies with positive results of C5a pathway inhibitor-based therapy [52].

5. COVID-19 and related topics during AUTO13

Due to importance of the topic, and based on hundreds of abstracts submitted to the congress in regard to COVID-19, the correlation between COVID-19 and autoimmunity was discussed in three main plains during AUTO13 as follows:

5.1. COVID-19 and autoimmunity

Given the huge impact the pandemic continues to have as it approaches its 3rd year, countless of autoimmune associations have been identified in literature. While the world is dealing with the aftermath of COVID-19 pandemic, AUTO13 served as the perfect stage to highlight the associations COVID-10 and autoimmunity share. Vojdani et al provided evidence for SARS-CoV-2 to be crowned as the 'Autoimmune Virus'. Due to its capability in triggering hyperstimulation of the immune system, the virus was linked to several autoimmune diseases, such as Kawasaki disease, Grave's disease, SLE, among many others [53]. Although the exact pathogenetic mechanism is still unknown, the study of Vojdani and colleagues indicated that SARS-CoV-2 infection stimulates the production of multiple autoantibodies which in turn may result in life-threatening autoimmune diseases [54]. Furthermore, the pulmonary intravascular coagulopathy (PIC) as a mechanism for arteriolar and venular territory thrombosis among patients with severe COVID-19 was introduced by McGonagle. In fact, SARS-CoV-2 tropism for alveolar type II pneumocytes was associated with the physiological immunothrombosis seen in COVID-19 patients. The failure of initial innate immune responses may trigger severe myeloid related inflammation in severe COVID-19 pneumonia, whereas it may remain confined to the alveoli in milder cases. Steroids, anti-cytokine therapy, and JAK inhibitors might be helpful in severe COVID-19 due to a possible moderation of lung tissue immunothrombosis in the post-viral replication phase of COVID-19, the author concluded [55]. Similarly, autoantibodies in COVID-19 and the association with autoimmune diseases, was presented by Baiocchi and researchers. Following the assessment of autoantibodies in 171 COVID-19 patients, the authors found an increased dysregulated levels of autoantibodies in the serum of patients with moderate or severe COVID-19 infection. This suggests that the virus causes a wider loss of tolerance than what was anticipated before. Riemekastan described COVID-19 as a heterogenous disease with varying symptoms and complications. In a systematic antibodies screening in patients with COVID-19, the authors identified anti-GPCR antibodies as natural components in the human body, however these antibodies production was disrupted in COVID-19. Furthermore, the levels of the antibodies isolated and the alteration patterns detected may reflect the disease severity as mentioned previously [54], the authors concluded. Zandman-Goddard et al argued that severe COVID-19 may be recognized as one of the hyperferritinemic syndromes based on several mechanisms and implications COVID-19 shares with the 4 members of the hyperferritinemic syndrome [56,57]. In addition to the elevated levels of ferritin in patients with severe COVID-19, the subsequent complications and high mortality in these patients point out toward a pathogenetic role ferritin may play in the disease. In fact, ferritin is not the only factor to serve as an indicator of prognosis for COVID-19 severity. Circulating calprotectin (cCLP) has shown to be a promising factor in evaluating the severity of COVID-19 due to the fact that cCLP is part of the innate immune response [58]. In this regard, the levels of cCLP among other factors were analyzed by Hoovels and colleagues in 136 patients with COVID-19. Interestingly, higher levels of cCLP were detected in severely ill patients and those who were admitted to the intensive care unit. In a different study of patients arriving to emergency department, a similar conclusion was drawn, where cCLP could be used as an early predictor for COVID-19 severity [59]. Thyroid autoimmunity and COVID-19 association was discussed by Kostoglou-Athanassiou who presented a 50-year-old patient who developed subacute thyroiditis 2 months following a mild SARS-CoV-2 infection, as well as a case of a 53-year-old male patient who developed subacute thyroiditis 3 days following COVID-19 vaccination. Both cases presented with high CRP and ESR and low TSH levels. Prednisolone 16 mg twice a day was given for 10 days, then tapered, alongside propranolol 20 mg twice daily. In both cases, the illness had gone into remission. One month after stopping prednisolone, the illness relapsed in the female patient. Multiple studies supported this claim, such as the first case to be described in the medical literature stating that a patient with slightly elevated heart rate and a sore and enlarged thyroid on palpation. Free thyroxine and free triiodothyronine were raised in laboratory tests, thyrotropin was undetectable, and inflammatory indicators and white blood cell count were higher. Neck ultrasonography revealed bilateral and widespread hypoechoic regions. The patient was diagnosed with sub-acute thyroiditis and started prednisone treatment with good clinical response. In 40 days, thyroid function and inflammatory indicators were returned to normal [60].

5.2. COVID-19 vaccines and autoimmunity

COVID-19 vaccines as well were addressed during AUTO13 based on the fact that several papers described the correlation between autoimmunity, autoimmune mechanisms, and manifestations with vaccines against COVID-19 [9,61]. For example, Novel autoantibodies induced by COVID-19 vaccines have been identified through engine protein arrays, according to Metzke. Still, clinical relevance needs to be confirmed [62,63]. Interestingly, interferon gamma release assay (IGRA) was suggested to be beneficial for testing the cellular response after SARS-CoV-2 vaccination, especially in immunocompromised patients such as those with steroid therapy. The findings were presented by Renaudineau and colleagues during the session based on their newly published data

[64].

With reference to adverse events following COVID-19 vaccines, in one study, a total of 28 adults were diagnosed with autoimmune disease among almost 361,000 recipients of at least one COVID-19 vaccine dose. Vasculitis was the most common condition with nine cases. Therefore, Hocevar and colleagues implied that COVID-19 vaccinations might be associated with the induction of autoimmune and autoinflammatory diseases [65]. Elsalti elaborated on the slight increase of myocarditis following COVID-19 mRNA vaccination, particularly among young males. The mRNA-1273 vaccine was shown to be associated with higher rates of myocarditis than the BNT162b2 vaccine. Nevertheless, in most of the cases the prognosis was good and cardiac function recovered well after a conservative therapy [66]. The involvement of hyperstimulation by the vaccine in the pathogenesis of myocarditis after mRNA vaccinations was underlined during the presentation [67]. Furthermore, Zoubi highlighted the autoimmune neurological adverse events seen after BNT162b2 mRNA vaccine administration. Bell's palsy was reported in this regard but concluded to have no major impact on public health [68]. In addition, a link between the ChAdOx1 vaccine and Guillain-Barre syndrome was postulated and requires further investigation, particularly in terms of the pathogenesis [69]. Albuquerque presented 4 cases of autoimmune hemolytic anemia in older patients following vaccination with mRNA COVID-19 vaccine and emphasized the importance of early monitoring of blood counts and markers [70,71].

Respecting drugs used in vaccinated individuals, it was shown that patients treated with B cell targeted therapies, especially rituximab, had lower rates of B cell response following COVID-19 vaccination, according to Fabris and colleagues. On the other hand, T Cell response among the majority of the patients was similar to that in the control group [72]. Moreover, Milo showed that multiple sclerosis (MS) patients treated with fingolimod or ocrelizumab had a lower humoral response to the second and the third mRNA COVID-19 vaccination compared to other disease-modifying therapies for MS. Patients who underwent fingolimod therapy had a diminished cellular response as well [73].

5.3. Post-COVID or long COVID

Some of the associations put on spotlight at AUTO13 were the ones in relation to Post-COVID syndrome which were explored in a dedicated session. Seida I. outlined an overview of the symptoms affecting various organ systems in Post-COVID syndrome [74]. The symptoms range from cough, chest pain, and dyspnea in the respiratory system, to neurological symptoms such as headache, difficulties in concentration, sleep disorders, and memory loss. Seida I. also highlighted a couple of mechanisms with one of particular interest to autoimmunity is the cytokine storm phenomenon which is characterized by a massive and disproportionate release of cytokines including IL 1, 6, 8, 17, and 1β, MCP1 and TNF. Cytokine storm and subsequent multiple organ failure have been addressed before in relation to SARS-CoV-2 infection [75]. Autoantibodies role in Post-COVID was a favorite among presenters with many trying to chart through their relationship [76]. Lassner and colleagues identified autoreactive antibodies in Long-COVID patients using engine healthy alignment. The study screened human sera of 20 healthy donors and patients with history of SARS-CoV-2 infection alongside long-term clinical symptoms utilizing engine array 1008 (15.000 human proteins; expression host: E. coli), to contrast autoantibodies in healthy individuals to SARS-CoV-2-induced autoantibodies. Anti-human-IgG-AP secondary antibody was used for detection. Positive signals were confirmed if duplicated signals were differentiable from background. Lassner emphasized that the presence of a reliable reference cohort is vital for successful identification of disease related autoantibodies. Among the talks about autoantibodies, some presenters focused on identifying certain antibodies of interest. Falk analyzed 32 healthcare workers with long term symptoms utilizing two sets of in-house developed planar protein arrays (untargeted array contains 42000 protein fragments representing 18000 human proteins. targeted array contains 1500 full-length extracellular or secreted proteins). Falk found 150 autoantibodies in the untargeted array and 130 in the targeted array, with 20 autoantibodies overlapping between the two groups. The most common antibody was anti-CFHR2 which was identified in 6/8 symptom groups. Cabral-Marques identified anti-GPCR autoantibodies targeting the chemokine receptors CXCR3 and RAS-related molecule AGTR1 (as having the strongest relationship to severe COVID-19 by comparing serum autoantibody levels of COVID-19 patients to healthy controls [54]. Given the large magnitude of associations between Post-COVID and autoimmunity some other relationships were explored that do not directly pertain to autoantibodies. Plaça showcased the overlap in immunological signaling pathways between COVID-19 and hemophagocytic lymphohistiocytosis (HLH) [77]. This reflected on the fact that a common dysregulated neutrophil-associated gene signature reflected a generalized hyperinflammatory states and associated with COVID-19 severity [78]. Finally, Kasperkiewicz in a systemic literature review emphasized that awareness of rare post-COVID-vaccine autoimmune bullous disease (AIBD) could prove vital to the patients management. Kasperkiewicz found that among 932 immunized individuals 5.7% presented with new onset AIBD, another 9.7% had AIBD flares 1 day to 6 weeks following the 1st or 2nd dose of the vaccine [79].

6. Autoimmune and Rheumatic diseases during AUTO13: (diseases 1–9)

6.1. Antiphospholipid syndrome

During AUTO13, the innovations in understanding and management of antiphospholipid syndrome (APS) caught a special attention. Since the presence and levels of antiphospholipid antibodies (aPL) have important role, Sciascia et al designed a study to test the hypothesis that high titers of aPL remain positive in time whereas low titers fluctuate. In their study, the researchers also evaluated the correlation between aPL and platelet bound C4d (PC4d) due to their association with thrombosis in SLE [80]. Antiphospholipid antibodies such as anti-cardiolipin, anti-ß2 glycoprotein I, antiphosphatidylserine/prothrombin complex antibodies, and PC4d were measured in consecutive samples for 5 years period. According to the analysis, high titers of aPL remained positive progressively, a finding that may help in early diagnosis and risk assessment. Moreover, since low to moderate correlation between aPL and PC4d was established, it may be used in evaluating the association with thrombosis in autoimmune diseases as an additive value. In the same manner, Cabrera-Marante and friends investigated the role of the non-criteria antiphospholipid antibodies in APS and their possible importance in patients negative for antiphospholipid antibodies of the Sydney consensus and lupus anticoagulant. The authors also included the differential clinical conditions of isolated positive patients for non-criteria aPL. A total of 838 patients who met the clinical APS classification criteria were evaluated for anti-PS/PT, IgA anti-ß2 glycoprotein I, aPL, and LA. Of the individuals enrolled, 314 were positive for at least one aPL, 137 met Sydney criteria, whereas 50 had anti-PS/PT, 71 had IgA anti-ß2GPI, and 54 had LA. The group concluded that non-criteria aPL might help in APS diagnosis and those with both LA and anti-PS/PT were found to have clearly different clinical characteristics [81]. Furthermore, Naranjo et al aimed to evaluate the association between circulating immune complexes (CIC), which are formed by ß2GPI and anti-ß2GPI, and APS related characteristics, since it is not included in the classification criteria of APS. In a multicentric study conducted by the group, 303 patients who met APS classification criteria were assessed for the presence of ß2-CIC alongside clinical characteristics and biomarkers relevant to disease activity. Interestingly, patients with ß2-CIC and thrombotic APS were found to be at higher risk of heart valve thickening and dysfunction, and thrombocytopenia compared to ß2-CIC negative patients and ß2-CIC positive patients with isolated gestational APS. As a result, the authors pointed out that ß2-CIC could serve as a possible biomarker for APS disease activity [82]. Moschetti retrospectively

examined a cohort of 415 consecutive patients with the diagnosis of thrombotic APS at four European centers. The study compared APL positivity in those who experiences both arterial and venous events verses those who did not and found out more triple aPL positivity in those who experienced it (65%) against those did not (39%) [83].

As the differential diagnosis of anti-lipid autoimmune diseases is challenging, a need of novel tissue-specific autoantibodies is urgent. Guerra-Galan et al conducted a study aimed to determine the incidence of myelin basic protein (MBP) antibodies on peripheral nerve and antiphospholipid antibodies in the serum of patients with neurological diseases. In their study, blood and nerve specimens from 77 patients with suspected neurological disorders were tested. Out of 77 patients, 27 were found to have positive MBP antibodies. In addition, 8 of the 27 patients had also positive aPL which were dominantly IgM and anti-ß2-glycoprotein. As antibodies against MBP have been formerly studied [84,85], their clinical and prognostic implications in neurological disease and APS is still to be determined.

In regard to COVID-19 and APS, both disease share many similarities in terms of vascular thrombosis and the presence of antiphospholipid antibodies. Gil Etayo et al conducted a prospective study over 360 COVID-19 patients and 143 healthy volunteers as a reference group. Measurement of aPL, anti-ß2GPI IgA, anti-phosphatidylserine/prothrombin IgG/M, and anti-SARS-CoV-2 antibodies was performed at the acute phase of COVID-19 and more than 12 weeks later. A significant difference in prevalence of aPL in COVID-19 patients and reference group was not observed however, the presence of aPL was found to be related to thrombosis. The aPL related thrombosis was detected considerably later than non-aPL-related thrombosis in COVID-19 patients. The authors concluded that at least two overlapping mechanisms in COVID-19 thrombosis could exist, one is the cytokine-storm related seen earlier and the second is aPL-related thrombosis found later in the disease course [86]. Moreover, COVID-19 patients with lung and systemic involvement presented with coagulation abnormalities such as increased D-dimer levels and prolonged prothrombin time as was highlighted by Cervera and colleagues. Even though patients are at increased risk of thromboembolic events; the incidence of such events are underestimated because of asymptomatic presentation and the inability to perform proper imaging [87]. In most of the autopsies performed to date, thrombotic microangiopathy has been detected as pulmonary thromboembolism and deep vein thrombosis. Cervera indicated that although this hypercoagulability state resembles APS and up to 87.7% of severe COVID-19 patients in intensive care unit (ICU) are found to have lupus anticoagulant in their bloods, presence of antiphospholipid antibodies and other related molecules have not been determined. For instance, patients with normal Beta2GPI did not suffer from respiratory failure neither had an increase mortality rate. The lack of Beta2GPI would interfere with regulatory function of coagulation and platelet aggregation, which makes it hard for patients to control thrombotic storm. Despite the fact that autoantibody involvement has not been proved, the situation would be said to resemble APS [88].

Presenting the target therapies in APS, Sciascia stated that while the therapeutic options for APS nowadays are restricted to long term anticoagulation with vitamin K antagonists; new potential targets which are under investigation would be promising in the future. However, the presenter also addressed the challenges in designing prospective randomized controlled clinical trials needed for the assimilation of these therapies to clinical practice [89]. In the same regard of treatment, and due to the disadvantages of long-term anticoagulant therapy, manifested as catastrophic APS (CAPS) and the so-called "non-criteria manifestations" (thrombocytopenia and autoimmune anemia); physicians were encouraged to search for possible disease modifying drugs. Since Doria et al reported that some of the SLE patients with APS on combined immunosuppressive therapy became antiphospholipid antibody negative, immunosuppressants were studied for this aim [90].

Tincani mentioned that hydroxychloroquine, with known antithrombotic effect, was found to decrease aPL levels significantly, but only in long term use. Moreover, belimumab was also shown to decrease aPL levels in SLE patients when used for the same period. As demonstrated in some case reports, rituximab was effective in persistent aPL associated with thrombocytopenia. In case of CAPS and microangiopathies related to aPL, the use of corticosteroids and immunosuppressants is recommended in guidelines. Lastly, inhibition of complement system by eculizumab and inhibition of mTOR pathway by sirolimus were suggested by experimental data and some clinical reports [91].

6.2. *Systemic lupus erythematosus*

Regulatory B cells (Bregs) have important features in both prevention and cure of many inflammatory and autoimmune diseases by regulating the proliferation of T cells and producing IL-10 for proinflammatory Th1 polarization. Since impairment of Bregs was observed in SLE, Jamin et al stated that treatment targeting Breg cells management have a great potential of effectiveness in SLE. In their study, the group explored glatiramer acetate (GA), a synthetic polypeptide used in inflammatory conditions and autoimmune diseases, which was found to stimulate healthy Bregs to reproduce and produce IL-10. Furthermore, B memory cells, which are the ones that GA binds preferentially, increase GA-dependent increased Breg cell activities. In conclusion, drugs such as GA may be useful as a therapeutic agent for SLE treatment [92]. Similarly, and as 6-sulfoLacNAc+ monocytes (SlanMos) are known as proinflammatory nonclassical monocytes involved in SLE [93]. Their dysfunction and recruitment to the inflammation site in SLE patients were reported by Schäkel and colleagues [94]. In the study of Alvarez et al, the authors found that encapsulated itacitinib in nanoparticles lowers the number of circulating SlanMo specifically suggesting that targeting SlanMos by nanoparticles would be of great potential for the treatment of SLE.

Recently the prognosis of SLE has improved due to the consistent use of immunosuppressive agents, better diagnostics, and milder disease detection. However, lack of suitable biomarkers indicating various pathophysiological processes and the intervention needed makes it difficult to medical community to figure out a personalized therapy for SLE patients. Moreover, the heterogenicity of SLE leads to less successful studies, strengthening the fact that “treat the target” approach is required to standardize treatment goals and identify the differences between patients [95]. All the aspects mentioned were presented by Schneider. The presenter also illustrated how remission of the disease is related to better quality of life, less pain, and less damage according to analyses of different studies from all over the world.

In some of the autoimmune diseases, the presence of naturally occurring autoantibodies to components of autophagy process is identified. Since their specificity, potential pathological features, and their relationship with clinical outcomes remains unclear, Muller et al investigated IgG autoantibodies which react with a group of cytoplasmic endosomal and lysosomal antigens and individual heat-shock proteins. The involvement of autoantibodies affecting autophagy process, which is abnormally increased in SLE, was observed in the study. Based on that, new connection between autophagy dysregulation and pathophysiology of lupus could be established [96]. Dysregulation in N-glycosylation of proteins in SLE and its relationship with pro-inflammatory immune reaction were discussed by Alves and friends. The samples of human kidney biopsies of lupus nephritis patients were collected and assessed for the alteration of glycosylation. Alves stated that lupus nephritis samples demonstrated unique mannose-enriched glycosylation pattern. The studied pattern is found typically in lower organisms and could be used as a predictor of chronic kidney disease with a specificity of 93%. Moreover, increased number of a specific T cell subsets was detected in vitro, found to sense glycosylated antigens, exerting its pathogenic activity [97]. The correlation of SLE with atherosclerosis was presented by Amital and colleagues. SLE patients were shown to pose higher risk to develop atherosclerosis [98]. Therefore, Shumilova et al designed a study to assess the association between serum atherogenicity of SLE

patients, disease activity and corticosteroid administration. According to the results, high atherogenic possibility was found in 90% of SLE patients compared to only 15% of the control group. The authors pointed out that serum atherogenicity in the group receiving corticosteroids were lower than in the non-corticosteroid group. In regard to SLE treatment, Putterman also discussed itolizumab in SLE in a phase 1B study and concluded that two subcutaneous doses of itolizumab up to 2.4 mg/kg SC were well tolerated, while the 3.2 mg/kg group had poorer tolerability, with 50% of patients discontinuing after the first dosage. A clinical trial conducted by Putterman and colleagues concluded that the drug appears to be safe and well-tolerated at a dosage of 0.4 mg/kg throughout a 4-week treatment period, according to data from the first cohort of patients.

Concerning lupus nephritis (LN), Putterman argued that soluble urine ALCAM reflects longitudinal renal disease activity in LN via obtaining serum and urine samples from patients with lupus nephritis and living kidney donor controls. Urinary ALCAM levels were substantially higher in LN patients (mean 4333.5 pg/mL) than in controls (mean 214.4 pg/mL), while serum ALCAM levels were not different. CD6 levels in the blood and urine did not alter as the illness progressed, indicating that the discrepancies were not attributable to hemodynamic changes or glomerular permeability loss. This means that urinary ALCAM levels are elevated in SLE patients with active LN and decline with clinical improvement [99]. These findings are consistent with the previous findings of the author [100]. In addition, state of the art on therapies used in LN management was presented by Roccatello. The presenter illustrated the current regimens used in the treatment of lupus nephritis starting with mycophenolate mofetil (MMF) and intravenous cyclophosphamide (CYC) but also mentioned the lack of robust treatment guidelines for refractory lupus nephritis. The challenges such as inducing the remission and reducing the steroid use in the treatment of the disease, which is present in more than 40% of the patients, were discussed as well [101,102]. A novel therapy, Intensified B-Cell Depletion Protocol (IBCDT) has shown promising results equal to the previously mentioned regimens with an additional advantage of significant decrease of glucocorticoid cumulative dose [103]. Despite the disappointing results of previous randomized controlled trials; IBCDT seems to serve as a new option for patient with severe disease [104]. In addition, the author addressed the challenges in treating refractory LN (RLN). Several drugs and therapies have been suggested such as B cell modulating therapies, proteasome inhibitors and calcineurin inhibitors [103]. Another promising approach, B cell depleting agents, such as obinutuzumab, showed increased renal response when it is used with the other standard of care drugs like mycophenolate mofetil [105]. Rituximab, another B cell depleting agent, is reported to decrease the probability of relapse even with patients are not on ongoing immunosuppressive treatment [106]. The newly stood out monoclonal antibody daratumumab, which influences cell adhesion and signal transduction in many immune cells via CD38 glycoprotein was discussed by the author [107].

6.3. Rheumatoid arthritis

As an innovative filed in medicine, machine learning was successfully implemented in RA as well. For instance, while RA is often diagnosed in late stages after irreversible joint damage has occurred, Shovman et al used machine learning tool to create an algorithm called PredictAI™ that can detect possible missed diagnosis of RA by the clinician. Out of the 2.5 million electronic records that were obtained from the Maccabi Healthcare Services in Israel, 340 cases were diagnosed with RA, by which the AI was able to identify 181 patients 1 year prior to the diagnosis made by the clinicians. Actually, the use of machine learning in other areas of RA such as predicting response to treatment and predicting remissions following biologic DMARDs have been described [108,109]. Furthermore, the so-called, the triad for developing RA: HLA-DRB1 stared epitope, a low educational level, and *Prevotella* was presented by Renaudineau. A total of 54 patients with RA and 31 controls were selected from the Tatarstan's cohort and tested for gut microbiota by 16S rRNA. The analysis of RA-associated factor included HLA locus variability (HLA-A/B/C/DQ and DRB1), cytokine polymorphism, haplomitotype determination, and a large panel of environmental factors. *Prevotella* spp. were overexpanded in stool samples from low educated individuals and among them HLA-DRB1-SE represented a risk factor for RA, the study illustrated. The contribution of oral and gut microbial species to the pathogenesis of RA was previously demonstrated [110]. The potential pathogenetic role of tetraspanin32 (TSPAN32), a member of the tetraspanin family, which is actively involved in the regulation of the immune responses in RA was discussed by Fagone. The presenter evaluated the TSPAN32 expression levels in circulating and synovial-infiltrating immune cells from RA patients as well as in immune cells from the IL1ra knockout (KO) animal, a mouse model of RA. At 1 and 4 months of age, splenic CD4+ T cells from IL1ra KO mice showed substantially less TSPAN32 expression. The remaining tetraspanin, however, showed no apparent modulation, with the exception of TSPAN4 and TSPAN31, which demonstrated a substantial increase in comparison to the wild-type mice. In addition, a significant downregulation of TSPAN32 was seen in the inflammatory HLA-DR+CD27- cells from RA patients compared to those with osteoarthritis. Lower expression of TSPAN32 in RA patients could help to initiate the arthritogenic immune responses, the results were concluded. Aspects of tetraspanin in RA were addressed before [111]. The role of antibodies against the fibrillar cartilage collagen type II (anti-CII) in RA was illustrated by Rönnelid. Levels of anti-CII in RA patients were shown to be high at the time of diagnosis and decrease thereafter during the first year. In addition, anti-CII-containing immune complex (IC) was found to induce the inflammatory cytokines. In another study, RA patients anti-CII-positive were presented as a distinct phenotype that, in many aspects, behaves differently from RA linked with ACPA in terms of clinical prognosis, HLA-DRB1* association, and relation to smoking history [112]. In contrast to the high disease activity at diagnosis, anti-CII-positive RA patients had an abrupt onset of the disease and a favorable prognosis. This raises the possibility that early detection of anti-CII, along with concurrent clinical signs of increased disease activity, may be linked to a transient inflammatory phenotype, given that anti-CII levels decline over the course of the first year [113]. Edwards explored the connections between brain and RA. It is well document that RA is not just a synovial joint disease rather it is a systemic disease with multi-extra articular involvements including the cardiovascular and respiratory systems, cognitive function, and other organ systems [114]. The recently discovered connection between RA patients and increased risk of brain related pathology, including stroke, dementia, and cognitive function also the positive outcomes of antirheumatic drug treatments have been mentioned by the author [115]. This connection could be used as a guide to discover the effects of chronic inflammation on dementia and cardiovascular disease, the authors suggested [116]. Vandormael discussed the novel antibody biomarkers that predicts absence of early and sustained disease remission and low disease activity after intensive first line therapy in RA. Participants in the CareRA study who failed to achieve early DAS28CRP remission following rigorous csDMARD treatment had their baseline serum tested for antibody reactivity to cDNA phage display libraries producing RA synovial antigens. In 179 baseline CareRA samples, the presence of antibodies to the identified University Hasselt, RA antigens was confirmed by ELISA and was linked with various criteria for remission during follow-up. According to the research, patients who did not achieve DAS28CRP or DAS28ESR remission at week 8, or who did not meet the criteria for RA had baseline antibody reactivity against 3 antigens, UH-RA.305, UH-RA.318 and UH-RA.329, which was significantly higher than that of RA patients who met these criteria. In patients who did not maintain prolonged illness remission, baseline antibody reactivity against the UH-RA.305/318/329 antigens was substantially greater. The authors discovered 3 antibody biomarkers that indicate a lack of response to

first-line RA medication which may help guide medical treatment choices. In the same regard of novel biomarkers, Heiss and colleagues presented their study on biomarkers of seronegative early RA. The authors used high-density peptide microarrays with many autoantigens and potential antigens transformed into >100.000 overlapping peptides, including all citrullinated and carbamylated variations, searching for new biomarkers. Many epitopes with a greater incidence in previously seronegative early-stage patients were identified. A peptide biomarker combination created by bioinformatic analysis and machine learning enabled for the accurate identification of early seronegative RA vs. healthy controls with 87% sensitivity and early seropositive RA vs. healthy controls with 94% sensitivity, respectively. Hence, the novel marker set has the potential to improve the early diagnosis of RA. Actually, the role of biomarkers in RA, particularly in decreasing false-negative results and aiding in the correct diagnosis of seronegative RA is of extreme importance [117]. Finally, Abali and friends investigated the rate of infections alongside the most common infectious side effects of baricitinib, a Jake kinase 1 and 2 inhibitor, used in the treatment of RA. The authors demonstrated that oral herpes together with herpes zoster were the most commonly encountered infections. A correlation was also found with higher doses of baricitinib. The immunomodulatory effect of baricitinib including cytokine effects on immune cells and the inhibition of numerous growth factors and cytokines such as IL-2, suppressing both innate and adaptive immune responses, were suggested as the most comprehensive mechanisms behind such side effects [118,119].

6.4. Systemic sclerosis

In addition to RA, biomarkers in systemic sclerosis (SSc) were addressed by Norman on their study about the comparative prevalence of 20 biomarkers simultaneously measured in Chinese and European systemic sclerosis patients using particle-based multi-analyte technology. The sera of 198 Italian and 266 Chinese SSc patients were examined by PMAT for autoantibodies to 20 autoantigens. The frequency of novel biomarkers such BICD2, was infrequently found in Chinese patients compared to European patients and confirmed earlier studies of greater prevalence of antibodies to RNP, Scl-70, and lower prevalence of ACA in Chinese SSc patients. Furthermore, biomarkers which can be used in diagnosis and prognosis of SSc take an important place in clinical research. It is documented that 90–95% of systemic sclerosis patients are positive for antinuclear autoantibodies (ANA) [120]. However, the sensitivity of ANA tests and presence of other autoantibodies in ANA negative SSc patients have been questioned. De La Cruz Trillo et al aimed to evaluate SSc patients who have tested negative for all autoantibodies by available commercial assay (LIA). A total of 293 patients were tested in terms of the presence of autoantibodies against topoisomerase I, centromere, RNA polymerase III, fibrillarin, NOR-90, Th/To, Pm-Scl, and Ku by LIA. From the patients examined, 69 patients were found to have negative antibodies by LIA and were further evaluated by using the gold-standard assay RNA immunoprecipitation (RNA- IP). Six of the seronegative patients (8.7%) were found to have anti-Th/To autoantibodies despite LIA pointing out the opposite. The authors tested ANAs in all patients by immunofluorescence (IIF). According to IIF results, a nucleolar pattern was detected in 16 (23.2%) of the seronegative patients. Interestingly, anti-Th/To were detected by RNA-IP in 37.5% of the seronegative patients with nucleolar patterns. Thus, the sensitivity of anti-Th/To autoantibody by LIA was measured to be around 14.3% at most. The authors concluded that the presence of anti-Th/To autoantibodies should be questioned in patients with a nucleolar IIF pattern even though they were negative by LIA. Another study for discovering new biomarkers of SSc was conducted by Geroldinger-Simic and colleagues. The authors performed a proteome-wide screening on sample pools of SSc patients to identify new biomarkers for detecting early fibrosis. A targeted antigen bead array was conducted to test the reactivity of the selected proteins with 55 SSc plasma samples and 52 matched controls. An increase in 8 fibrosis-associated autoantibodies in SSc patients compared to the control group was noticed. Among the autoantibodies isolated, 2 were suggested to be used as biomarkers for fibrosis in SSc patients, namely anti-phosphatidylinositol-5-phosphate 4-kinase type 2 beta (anti-PIP42K2B) and anti-AKT Serine/Threonine Kinase 3 (anti-AKT3) antibodies [121]. Intense research not only for discovering new biomarkers but also revealing the association of identified biomarkers with the pathogenesis of SSc is being conducted. For instance, Lande and friends designed a study to reveal pathogenic properties and biomarker potential of the non-allelic variant of Chemokine (C-X-C motif) ligand 4 (CXCL4). For a long time, it has been known that CXCL4 autoantibodies in patients with SSc are used as biomarkers for SSc progression [122]. In 2018 Lande et al elucidated that nucleic acid complexes, formed by chemokine (C-X-C motif) ligand 4 (CXCL4) and DNA stimulate plasmacytoid dendritic cells (pDCs) to produce IFN-I [123]. Additionally, previous research showed that CXCL4-DNA complexes trigger B cells to become plasma cells secreting autoantibodies against CXCL4 [124]. Recently, the authors suggested that CXCL4-L1 which is formed by three amino acid substitutions in COOH-terminal of CXCL4 could become an SSc-autoantigen in long-lasting SSc. Most importantly, the authors demonstrated that anti-CXCL4 antibodies implement the interferogenic properties of CXCL4-DNA complexes on purified human pDCs forming a vicious circle in the pathogenesis of SSc mediated through CXCL4 [125]. Recently, autoantigens that trigger inflammation in SSc were questioned to be mutated cancer proteins due to the increasing association of secondary malignancies in SSc [126,127]. Gniadecki and colleagues analyzed skin biopsies from 8 patients with early progressive SSc with whole-exome sequencing to detect gene mutations. The authors found 1997 genes that were mutated in at least two SSc patients. Among the mutated genes, 39 were cancer driver genes that take the role in DNA repair, genome stability, and chromosomal histone modifications. Interestingly, similar findings were described before [128]. In terms of treatment, the mechanisms and effects of ibrutinib, tyrosine kinase inhibitor, by inducing low affinity B cells for DNA-topoisomerase I in systemic sclerosis (SSc) was presented by Sakkas. Furthermore, the drug inhibited fibrosis in a mouse SSc model. Of importance, the induction of regulatory T cells with low-dose IL-2 administration and JAK/STAT pathway inhibition in SSc mice improved fibrosis. The findings doubtlessly suggest new potential therapeutic agents for SSc such as ibrutinib [129].

6.5. Sjogren's syndrome

In a cross-sectional study through health maintenance organization (HMO) electronic records in Israel, Ben-Shabat investigated the linkage of anti-RO and anti-LA detected in Sjogren's syndrome with cardiac arrhythmias. All participants who tested positive for anti-Ro/anti-La antibodies between the years 2002–2019 were included and compared to controls. The study, which included 17,231 anti-Ro/La seropositive subjects and 84,368 controls, found that anti-Ro seropositive patients had higher rates of conduction disturbances and rhythm disturbances, while patients who were only anti-LA positive did not show any significant association with cardiac arrhythmias. Another study demonstrated that the risk of long QT syndrome (LQTS) was significantly increased in subjects with circulating anti-Ro/SSA antibodies, regardless of a history of overt autoimmune disease, raising the intriguing possibility that these autoantibodies may contribute silently to a number of cases of ventricular arrhythmias and cardiac arrest in the general population [130]. Additionally, maladaptive autophagy in the pathogenesis of autoimmune epithelitis in Sjogren's syndrome via primary salivary gland epithelial cells (SGECs) isolated from minor salivary glands was discussed by Colafrancesco. SGECs are key cellular drivers in the pathogenesis of Sjogren's syndrome. The SGECs isolated from minor salivary glands of patients with Sjogren's syndrome or sicca syndrome were evaluated by flow cemetery and immunofluorescence to assess autophagy, apoptosis, and activation. Actually, the activation of SGECs and

the mirroring of histological severity in Sjogren's syndrome by inflammation was reported by the author [131]. The findings suggest that autophagy is a key player in the pathophysiology of Sjogren's syndrome which would serve as a potential treatment target. Autophagy as a pathogenetic mechanism of autoimmune epithelitis was supported by another paper [132], enhancing the notion that, independent of the origin, metabolic changes of the targeted epithelial cells in Sjogren's syndrome may induce an immunogenic phenotype.

Coustal also discussed the overlap between Sjogren's syndrome and ANCA-associated vasculitis (AAV). The study involved 40 patients from 30 different articles, in addition to 4 new local patients. In individuals with granulomatosis with polyangiitis, AAV was most commonly associated with renal involvement (35/44 patients, 79.5%), with anti-MPO antibodies being the most common. Raynaud phenomenon and related auto-immune illnesses were found to be considerably more common in the non-granulomatous AAV group [133]. Multiple other studies supported this claim, stating that AAV not uncommonly occurs with Sjogren's syndrome [134]. In the same topic of overlapping, Marketos and friends suggested the possibility of using SSc-specific autoantibodies in the diagnostic work-up and classification of Sjogren's syndrome. While several studies suggested sicca symptoms are frequent manifestation of SSc [135,136], Marketos and friends investigated the presence of SSc-specific autoantibodies in patients with sicca symptoms. In their study, 216 patients with sicca symptoms were tested for SSc-specific autoantibodies such as PDGFR, Scl-70, Ku, Th/To, NOR90, RP11, fibrillarin, RP155, PM/Scl, and CENP. Around 20% the enrolled patients had increased titers of SSc-specific autoantibodies, whereas 23% had moderately elevated titers. In other words, more than 40% of the patients tested positive for SSc-specific autoantibodies in total. Furthermore, an association between high titers of SSc-specific autoantibodies and minor salivary glands (MSG) biopsy positivity was demonstrated. This result raised the possibility of using SSc-specific autoantibodies in the diagnostic work-up and classification of Sjogren's syndrome [137].

6.6. Chronic fatigue and pain

Characterized by widespread chronic pain along with fatigue, cognitive dysfunction and sleep disturbances, the etiology and pathogenesis of fibromyalgia are not clearly defined [138,139]. The dorsal root ganglion (DRG) was proposed by Martinez-Lavin as the major site responsible for pain in patients with fibromyalgia by which stress contributes to converting stressful impulses into neuropathic pain. Moreover, physical trauma and autoimmunity have also been linked to fibromyalgia through different mechanisms affecting DRGs. For instance, physical trauma in rodents caused nerve growth factor overexpression inducing DRG sympathetic nerve sprouting leading to abnormal connections with the nociceptive system. The involvement of autoimmune mechanisms in fibromyalgia where the DRG neurons serve as a target for antigen specific antibodies and subsequent DRG inflammation and pain has been extensively studied by the author [140]. Likewise, fatigue is experienced by 53–80% of patients with SLE and often one of the primary symptoms affecting the quality of life. The etiology of fatigue in SLE is believed to be multifactorial [141]. Aringer et al addressed fatigue in SLE and its relation to physical activity and the use of immunomodulatory drugs. In a study including 27 SLE patients, 20 experienced fatigue which was improved by the use of belimumab. However, it took almost one year for 8 patients to report complete disappearance of fatigue. The effects of belimumab on fatigue in SLE patients was previously reported as well as physical activity, as patients who reported more physical activity had less fatigue than those who did not [142]. Furthermore, the difference in fatigue in female patients with rheumatic disease prior and after pregnancy was studied by Roussou and friends. Ten women with different rheumatic diseases were asked to grade their fatigue before pregnancy, during pregnancy, and throughout the course of their illness. Women with rheumatic diseases experienced an increase in fatigue by 26% during pregnancy.

Worldwide, 20% of adults are estimated to have chronic pain with an additional 10% added each year [143]. Taking into consideration the unclear etiology, and the fact that patients do not respond to monotherapy, the burden of chronic pain related syndromes is continuously increasing [144]. The WHO-ICD 11 recently classified unexplained pains as chronic primary pain. Goebel and colleagues in an aim to search for the cause of unexplained chronic pain, identified autoantibodies in 4 different chronic primary pains which are: complex regional pain syndrome (CRPS), fibromyalgia syndrome, chronic post-traumatic limb pain, and non-inflammatory joint pain associated with rheumatoid arthritis. Interestingly, the passive transfer of the autoantibodies isolated from patients with the syndromes mentioned into mice caused various intensities of pain [145,146]. Similar findings were demonstrated by the author in regard to fibromyalgia [147].

6.7. Vasculitis

Vasculitides are no strangers to being discussed during the AUTO13 due to its relation to autoimmunity and the increase incidence over the past two decades [148]. Considering the era of the COVID-19 pandemic many speakers highlighted the impact the pandemic had on vasculitis. Hocevar and colleagues contrasted systemic vasculitis diagnosis before and during the pandemic of COVID-19 at secondary/tertiary medical centers. The authors found similar frequencies in most vasculitis except ANCA-associated vasculitis which was diagnosed 3 folds more during the pandemic when compared to the frequency of diagnosis prior to that [149]. Similarly, Irure-Ventura retrospectively compared ANCA vasculitis cases in 2019 to 2021 at University Hospital Marqués de Valdecilla. The authors registered a total of 35 patients in 2021 compared to 15 in 2019. In 2019, 73.3% of the patients had Anti-MBG, while only 13.3% had Anti-PR3 antibodies. In 2021, 45.7% and 42.9% presented anti-MPO and anti-PR3 antibodies, respectively. Irure-Ventura found that 27 out of 35 patients (77.1%) developed ANCA after receiving SARS-CoV-2 vaccine, with 88.6% of the cases receiving the BNT162b2 vaccine, suggesting that the increase could be attributed to the vaccine [150]. In the same regard, Gragnani recruited cryoglobulinemic vasculitis (CV) patients at 11 Italian referral centers to understand the impact of the pandemic and vaccination on their disease course. CV diagnosis, clinical and serological parameters, COVID-19 tests, and vaccination immunogenicity were carried out in compliance with contemporary techniques. Four-hundred-thirty CV patients (130 M; mean age 70 $\pm$10.96 years) were selected from February 2020 to October 2021. COVID-19 prevalence was found to be larger in CV patients compared to the Italian general population ($p < 0.005$). Around 87% had the vaccine administered and 50% received a booster dose. Disease flares/worsening following the vaccination [151] were less frequent than those associated to COVID-19 ($p = 0.0012$). CV patients displaced worse vaccination immunogenicity compared to controls ($p < 0.05$), and higher no-response rate after the booster. In addition, the mortality was higher in COVID-19 patients in comparison to ones without ($p < 0.01$) and age higher than 60 years corelated with worse COVID-19 outcome. Gragnani found CV patients at a higher risk for developing COVID-19 and more likely to have severe disease. Nevertheless, the author concluded that vaccines possessed good safety profiles in CV and the flares/side effects were lower in comparison to actual COVID-19 disease.

Some authors highlighted new understandings of mechanisms involved in the pathogenesis of certain vasculitis. Cavalli investigated the role of Trained Immunity (TI) in Giant Cell Arteritis (GCA) by contrasting monocytes from a large cohort of GCA patients to age and sex matched healthy donors who underwent polyfunctional determinations. GCA monocytes exhibited molecular features of TI including typical metabolic changes (increased glycolysis and glutaminolysis through the TCA cycle), epigenetic alterations that promoted proinflammatory gene transcription, and enhanced IL-6 synthesis with inflammatory change. Immunohistochemistry displayed that GCA lesions serve as highly glycolytic microenvironments, and pharmacologic inhibition of

glycolysis with 2-deoxy-glucose lowered IL-6 production. The study emphasized the role of maladaptive trained immunity in the pathophysiology of GCA [152].

Van Eeden contrasted patients suffering from MPO-ANCA with fatigue to non-fatigued patients and healthy controls, by a study which looked at Mitochondrial gene expression (Dloop, ND4, CyB) via qPCR. Cell free mitochondrial DNA integrity was determined by qPCR. Flow Cytometry with Annexin V (AnV) and Propidium Iodide was utilized to assess cell death. Expression of ND4 and CyB was significantly lower in fatigued MPO-ANCA patients in comparison to healthy controls. The mtDNA integrity was increased in fatigued MPO-ANCA patients in relation to both healthy controls and non-fatigued MPO patients. Cell death evaluated by AnV mean fluorescent intensity was higher in fatigued MPO-AAV patients, than in non-fatigued patients and healthy controls. The results allowed Van Eeden to emphasize the correlation between AAV and comorbid myalgic encephalomyelitis/chronic fatigue syndrome and attributed it to mitochondrial signature affecting the electron transport chain resulting in mitochondrial dysregulation and increased cellular death [153].

De novo treatments were suggested for vasculitis during the session on vasculitis. Fenoglio examined clinical trials on the use of Avacopan (formerly known as CCX168), a CV5a receptor inhibitor, for the treatment of ANCA-associated vasculitis. The assessment showcased safety over a sizable range of doses compared to glucocorticoid-based therapy. Moreover, when combined with cyclophosphamide or rituximab, Avacopan was similar in sustaining remission at 26 weeks and superior at 52 weeks [154].

6.8. Myositis

Holc demonstrated that Slovenian patients with idiopathic inflammatory myopathy (IIMs) had higher mortality rates compared to the general population in Slovenia during a 16-year observation period. The first year following diagnosis was characterized by 7 times higher mortality rate [155]. Vojinovic and colleagues found no close link between creatinine kinase (CK) levels, various types of IIM, and myositis-specific autoantibodies. However, some subtypes of dermatomyositis could be defined by histological differences [156]. According to Pedretti and colleagues the use of line blot has been useful in detecting previously undetected myositis-specific autoantibodies. The use of commercial tests (line blot) for IIM may be useful in upgrading the diagnostic possibilities for the diseases, the authors concluded. Interestingly, as presented by Garcia- Bravo, myositis-associated autoantibodies occurrence varied between the years 2020 and 2021, possibly due to both SARS-CoV-2 infection and vaccination. For instance, anti-MDA5 was the most common antibody detected in 2020, while anti-PL7 was most common during 2021 [157,158]. In the same regard, case reports of anti-MDA5 antibody dermatomyositis after allogeneic hematopoietic stem cell transplantation have been described [159]. Urban described a 63-year-old female patient with a history of acute myeloid leukemia. Though Graft-versus-Host Disease (GVHD) may be the reason for the autoantibodies detected, but primary dermatomyositis should be considered as well, the presenter suggested.

The association between autoimmune diseases and pulmonology is not uncommon as the first manifestations of a connective tissue disease could be interstitial lung disease (ILD). Thus, a cooperation between pneumologists and rheumatologist is of great importance. Looking for myositis-specific (MSA) or myositis-associated autoantibodies (MAA) in ILD patients may be required. A study presented by Angeli showed that MSA/MAA were found in 37/84 sera (44%) in patients that had a pneumological diagnosis.

6.9. Neurology and autoimmunity

Autoimmunity manifests in the central nervous system in a plethora of different ways. Therapeutic targets in the CNS attracted the most attention among speakers. Milo discussed recent studies showing the vitality of utilizing high efficacy treatment early in multiple sclerosis disease course for reducing disability accumulation and improving the overall course of the disease [160]. Furthermore, Beckers examined the importance of B cells in multiple sclerosis by underlining the success of B cell depletion therapies. The authors highlighted the role of B-cells beyond antibody production, which is characterized by cytokine secretion, and T-cell stimulation by antigen presentation and stimulation. A particular B-cell of interest was the IgD-CD27- double negative (DN) B which were shown to be elevated in the peripheral blood and CSF of MS patients. They potentially induced T-cell response and produced cytokines such lymphotoxin-α and tumor necrosis factor-α DN B also to resemble mature class switched memory B cells as they expressed developmental markers (CD5, CD10, CD38) and Ig isotypes (IgM, IgA, IgG). DN B cells also expressed LFA-1, VLA-4, and ALCAM alongside chemokine receptors (CXCR3 and CXCR5) allowing migration to the CNS. Moreover, DN B showcased migration potential towards the pro-inflammatory chemokines C-X-C chemokine ligand (CXCL)10 (CXCR3 ligand) and CXCL13 (CXCR5 ligand). T-box transcription factor T-bet expression was displayed in 22% of MS DN B cells [161]. This allowed Beckers to highlight the importance of research into utilizing these DN B cells as a potential target for novel therapies. Lazaridis examined the therapeutic potency of targeting human nAChR (thought to be the most targeted receptor in myasthenia gravis (MG)) α1 subunit extracellular domain (α1-ECD) in MG. The domain contains several MG T and B cell epitopes, using a mutated form of α1-ECD with increased solubility. The evaluation involved in vivo studies in a rat experimental autoimmune MG (EAMG) animal model, induced by immunization with the α1-ECD providing suitability for testing antigen-specific treatments. Intravenous treatment with α1-ECD resulted in sizably decreased experimental autoimmune myasthenia gravis symptoms in a dose and time dependent manner. The restoration of tolerance against certain autoantigens as an exciting prospect in treating MG was emphasized [162]. Moreover, Bruttel utilized activation induced marker (AIM) bios to induce human AQP4-specific regulatory T-cells which served to prevent neuroinflammatory disease, this allowed the study to highlight the importance of Aquaporin-4-specific AIM Bios in targeted immunosuppression in neuromyelitis optica spectrum disorders [163].

Interestingly, Einstein found that physical exercise modulates encephalitogenic T-cell responses allowing it to modify the pathophysiology of autoimmune diseases in the CNS. Physical exercise was also suggested to be involved in neuroprotective mechanisms. The importance of researching the optimization of physical exercise to achieve neuroprotection [164], was concluded by the author. Song examined the role of hydroxyfasudil (HF) on oxidative stress in experimental autoimmune encephalomyelitis (EAE) mice and its possible mechanisms. The study found no changes in BV2 cell viability with HF concentration of 0–15 μg/ml. HF lowered the clinical scores of EAE mice, improved the inflammation and demyelination of spinal cords, decreased oxidation products ROS, RNS and MDA, increased antioxidant enzymes SOD, CAT and GSHPx, and increased the expression of Nrf2 and HO-1 in spinal cords of mice. Song concluded that HF alleviated the pathology and clinical symptoms of EAE mice. This improvement may be associated with the activation of the nrf2/HO-1 signaling pathway by HF, allowing HF to inhibit oxidative stress. Finally, Ma talked about the anti-inflammatory effect of Fasudil and its role in improving remyelination via astrocytic transformation to A2 phenotype, a mechanism which might be promising for multiple sclerosis patients [165].

From therapeutic targets to potential pathophysiologic mechanisms, some speakers underlined potential ways in which autoimmunity damages the CNS. Mortiz analyzed autoantibody profiles in patients with sensory neuronopathy (SNN) utilizing two protein arrays (ProtoArray covering 7,634 human proteins for 38 SNN patients and 14 controls (7 other neuropathies, 7 healthy controls [HC]); HuProt array covering 15,797 human proteins for 12 SNN and 31 controls (22 other neuropathies, 9 HC). The authors performed overrepresentation

analyses (Reactome database, PantherDB) and cytokine profiling (Bio-Plex ProTM Reagent Kit III). SNN sera was found to be associated with far more proteins of the immune system pathways than the controls. These pathways included the innate and adaptive immune systems alongside cytokine signaling system. Anti-FGFR3-positive [166] patients were more reactive with immune system proteins than anti-FGFR3-negative patients, in relation the numbers of both targeted proteins and overrepresented pathways. IFN alpha-2 and TNF alpha levels were higher in anti-FGFR3-negative than in -positive patients.

7. Pregnancy and pediatrics during AUTO13

7.1. Pregnancy and autoimmunity

During pregnancy, patients with autoimmune rheumatic diseases often refuse treatment since they think drug administration would cause any damage to their future babies, Tincani reported. Moreover, there are evidence showing that disease activity in pregnancy could cause an increase in both fetal and maternal complications as demonstrated by Mecacci et al [167]. While only some drugs such as methotrexate, cyclophosphamide, and mycophenolate have teratogenic activities; their use in pregnancy is limited and most of the therapeutic agents used in autoimmune rheumatic diseases do not cause any malformations but may have few pregnancy complications [168]. Systemic autoimmune thrombosis and APS may lead to miscarriages and abortions still these diseases are originally treatable, as reported by Galarza-Maldonado. According to EULAR recommendations, management of APS can be divided in three groups: low doses of aspirin, low-molecular-weight heparin and in some cases, systemic glucocorticoids and intravenous immunoglobulins [169]. During personalized selection of treatment options, inflammatory autoimmune mechanism of APS and anti-inflammatory and immunomodulatory actions of drug should be considered, the presenter concluded. During pregnancy as well, pre-eclampsia, hypertension, and proteinuria, starting from the second half of the pregnancy, is a complication which is thought that various complement factors contribute to. Dijkstra and friends hypothesized that decreased C1q in vascular remodeling and Factor H (FH) or their dysregulation by autoantibodies may play a role in the pathogenesis of preeclampsia. Serum C1q and FH concentrations were higher in control pregnancies when compared to non-pregnant women. There has not been significant difference between control pregnancies and pre-eclamptic pregnancies in term of serum C1q nevertheless, serum FH levels were found to be decreased in preeclamptic women as opposed to control pregnancies. Furthermore, there was no difference established in anti-C1q and anti-FH between control pregnancies and women with preeclampsia [170]. Antiphospholipid antibodies (aPL) are well-established factors that might lead to adverse pregnancy outcomes (APO) by which anti-thyroperoxidase antibodies (aTPO) may act as a risk factor [51,171]. Lini and colleagues searched for the contributory role of aTPO in aPL positive pregnant women. A total of 53 women confirmed for aPL positivity and aTPO status before the conception were followed-up for APO as well as thyroid function tests. No significant difference could be found between aTPO positive patients and negative ones in terms of APO frequencies in which individualized prophylactic treatment may play a role. Likewise, in terms of thyroid diseases, Carolis et al conducted a study to assess thyroiditis prevalence in pregnant patients with autoimmune diseases and pregnancy outcomes related to thyroiditis. The test for thyroid antibodies, anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies, were performed in two groups of patients, control group of healthy pregnant women and pregnant women with autoimmune diseases. The positivity rate of thyroiditis in women with autoimmune diseases were 17.5%, though thyroiditis has been detected 5.5% of women in control group. The results suggested that thyroiditis in patients with connective tissue diseases have more prevalent deleterious outcomes such as early delivery and low birth weight which was not the case among thyroiditis in SLE and APS women [172].

Another interesting domain during pregnancy, inborn stress vulnerability is claimed to lead to pathological consequences in the developing nervous system of the baby via triggering maternal immune activation (MIA) and modifying placental homeostasis [173,174]. Pinhasov and friends demonstrated that stress-vulnerability induces MIA and results in adverse consequences of developing nervous system of the fetus via affecting hypothalamic-pituitary-adrenal (HPA) axis. The authors used mouse models of social dominance (Dom) and submissiveness (Sub) reflecting stress-vulnerable (Sub) and stress-resilient, respectively. The authors examined the response of two mice groups to the viral mimetic Poly(I:C). An exacerbated pro-and anti-inflammatory cytokine response in pregnant Sub mice compared to pregnant Dom mice was found. This result indicated that in Sub and Dom mice exhibited a differential MIA response to virus. Then, the authors evaluated the offspring of the Sub and Dom mice in terms of neural system. prenatally Poly(I:C) exposed Sub and Dom offspring were challenged by NMDA receptor antagonist, MK-801 (0.5 mg/kg; i.p.). The results indicated that prenatally Poly(I:C) exposed Sub offspring showed increased sensitivity against an acute challenge with MK-801 compared to Dom offspring. Thus, the authors concluded that the inherited stress vulnerability may reprogram the glutamatergic signaling which can be further potentiated by prenatal viral exposure [175].

7.2. Pediatrics and autoimmunity

As for childhood and autoimmunity, both have crossed paths in different forms and ways. An interesting study about effects of SSc in pregnancy and offspring of patients with SSc was presented. Pedretti and colleagues highlighted that although successful pregnancy rates among patients with SSc have been greatly improved, the outcome of children born to SSc mothers remains elusive [176]. The group aimed to evaluate the neuropsychiatric outcome of children whose mothers were diagnosed with SSc before or after pregnancy. The patient cohort consisted of 70 women who have given 108 live birth. The authors used the ad-hoc questionnaire to measure the neurodevelopment of children. Among 88 children who continue the follow-up, 36% were reported to have at least one neuropsychiatric alteration. Moreover, children were classified into 3 groups based on the onset of SSc in the mothers SSc: a. born >10 years before SSc onset; b. born within 10 years from SSc onset and; c. born after SSc onset. Results elucidated that neurodevelopment alteration was more common in children born to women within 10 years of SSc onset compared to other groups suggesting the effects of subclinical/untreated maternal disease on the neurodevelopment of children. In addition, children from the same group had neurologic disorders occurring in early phases of life such as childhood and scholar age. In contrast, disorders in adolescence were more frequently encountered in those born to women after SSc was diagnosed. In addition, reduced peripheral basophils in pediatric patients with SLE, given by Poddighe opened the pediatric session. While it has been suggested that circulating basophils can be reduced in adult SLE patients [177]; Poddighe and colleagues discussed the possibility this is also the case in the pediatric population. In their study, 55 pediatric patients were evaluated, and the conclusion was that, when compared to children with another rheumatic disease or non-rheumatic chronic disorders, children with SLE demonstrated a statistically significant drop in basophil counts. However, the pathophysiological and clinical significance of the findings were unclear; therefore, further clinical studies and multi-parametric analysis are required. Sepiashvili discussed the pediatric reference limits for 10 commonly measured autoimmune disease markers, where the CALIPER cohort for healthy children and adolescents was used to support the interpretation. Anti-dsDNA (26/119; 22%), anti-Sm (16/121; 13%), anti-RNP (1,120; 0.8%), anti-SSB/La (0/120; 0%), anti-Ro60 (0/122, 0%), anti-Ro52 (0/121, 0%), anti-cardiolipin IgG (105/117, 90%), anti-MPO (29/118, 25%), and anti-PR3 (11/119, 9%), all 10 markers had pediatric reference limits and

associated 90% confidence intervals that were determined to be lower than the assay cut-offs of the manufacturer [178]. The establishment of robust pediatric reference limits for ten routinely used clinical autoimmune markers would allow for enhanced laboratory evaluation of children patients utilizing this assay platform throughout the world, was concluded by the author. Uziel showcased results of the effectiveness of the BNT162b2 mRNA COVID-19 vaccine among adolescents with autoimmune inflammatory rheumatic disease (AIIRD) by using a big dataset from the largest healthcare organization in Israel. In an observational cohort the BNT162b2 mRNA vaccine was found highly effective in adolescents with AIIRD, similar to healthy controls. The AIIRD group had a seropositivity rate of 97.3%, compared to 100% in the control group. Anti-S1/S2 antibody titers, on the other hand, were much lower in the AIIRD group, which was similar to adults with AIIRD [179].

8. ASIA during AUTO13

The scientific evidence of the existence of ASIA was demonstrated by Cohen Tervaert. For instance, silicone incompatibility syndrome or breast implant illness which cause characteristic systemic adverse effects in almost one-quarter of women after the implantation, serve as a real-life evidence [180]. The author urged that in the future, the use of SBI should be replaced by using autologous material. Likewise, Halpert and colleagues shared their findings of an increased risk of autoimmune diseases in women with SBI [181]. Due to the fact that autoantibodies found were related to the autonomic nervous system, the authors introduced the term “autoimmune dysautonomia”. The levels of the autoantibodies were shown to have direct correlation with the symptoms seen in women with SBI such as depression, cognitive impairment, and sleep disturbances [182]. In the same regard, Burja et al presented a case report of a 35-year old female with a breast implant who had an adverse immune reaction to silicone. The course of the disease was exacerbated by COVID-19 vaccination eventually provoking vasculitis of granulomatosis with polyangiitis type. Another case report, described ASIA syndrome after silicone breast implant in a patient with familial history of autoimmune thyroiditis, was presented by Plasvsic et al. The authors recommended more precautious approach when considering silicone implants in such patients. Similarly, Churilov presented a year of follow-up over more than 100 female patients who had aesthetic/reconstructive breast implants. By the end of the year there was an increase in the number of patients that fulfilled the criteria for ASIA syndrome [183]. One of the measured autoantibodies was anti-TSHR, which was significantly elevated following the procedure. This was most probably attributed to its adjuvant effect in causing anti-thyroid autoimmunity and thus deeper consideration should be given to SBI, the author recommended.

In addition to silicone, vaccines as well were correlated to the development of ASIA. Although mRNA-based vaccines are produced through a different technique than the conventional vaccines, autoimmune symptoms of ASIA have been reported in individuals vaccinated against COVID-19 [184]. The paper was presented by Jara and friends addressing ASIA following COVID-19 vaccination [185]. Despite the fact that vaccines benefits outweigh the risks of ASIA, the symptoms should be taken into consideration and furtherly investigated.

The autonomic nervous systems alterations seen in patient with COVID-19 were discussed by Shoenfeld. Almost 20 autoantibodies, against GPCR molecules of the autonomic nervous system and renin-angiotensin-aldosterone system, related to the severity of the disease were identified [186]. Moreover, Shoenfeld explained how ASIA syndrome has prevailed in individuals following vaccination due to the use of adjuvants such as aluminum [187]. Shoenfeld addressed the mRNA vaccines developed against COVID-19 and used for the first time during the pandemic as a matter of indicating that better and safer methods of vaccine development could be found when large scale funds could be provided [188]. The famous say of Shoenfeld, which is the base of autoimmunity, “everything is autoimmune, until proven otherwise”, concluded the presentation [189]. Furthermore, autonomic dysfunction and small fiber neuropathy triggered by vaccination leading to post-vaccine syndrome in genetically susceptible patients, was discussed by Martinez-Lavin. The similarities seen in Post-HPV vaccination syndrome and other autoimmune illnesses such as macrophagic myofasciitis (MMF) and Gulf-War Illness, were highlighted by the author [190].

In an aim to expand our understanding and to aid in better diagnosis and treatment of autoimmune diseases, Mahroum and Shoenfeld presented their work on introducing a new encompassing term called “autoimmune autonomic dysfunction syndromes”. According to the authors and evidence presented, this umbrella term would give a comprehensive pathogenetic explanation to complex regional pain syndrome, fibromyalgia, chronic fatigue syndrome, silicone breast implants related symptoms and post-COVID syndrome; all which share similar symptoms and course of pain [184].

9. Infection and autoimmunity during AUTO13

The long and strong correlation between infections and autoimmunity necessitated, as usual, a dedicated session for this important topic. At the beginning, an update on IVIG therapy in COVID-19 was delivered by Goddard-Zandman. It is well documented that IVIG is a useful, safe, off-label medication that can be used for long-term treatment for a number of autoimmune illnesses by which IVIG has been shown to reduce immune responses [191,192]. IVIG comes in a variety of formats such as specific IVIG (sIVIG), and subcutaneous IVIG (scIVIG). Recently, the use of IVIG, both sIVIG and scIVIG, in COVID-19 was suggested. IVIG therapy has shown to be effective to improve the outcomes of patients with severe COVID019, and also safe in pregnant women with COVID-19 [193,194].

Alwani presented an update on streptococcal infection and autoimmunity. Acute rheumatic fever (ARF), acute post-streptococcal glomerulonephritis (APSGN), and pediatric autoimmune neuropsychiatric disease associated with streptococcal infection (PANDAS) as the autoimmune sequelae of the group A streptococcal infection [195], were discussed. The presenter stressed the fact that the autoimmune mechanism behind ARF could be viewed as the base for understanding infection and autoimmunity. Interestingly, patients with the streptococcal autoimmune sequelae co-infected with COVID-19 were shown to have more severe course of COVID-19. Furthermore, the correlation between ASIA and the 2 types of pneumococcal vaccine (namely PPSV23 and PCV13) was highlighted during the presentation. Likewise, the correlation between parvovirus and autoimmunity was illustrated by Esirgun. Three significant facts serve as a basis for a potential connection with autoimmunity: 1. the production of parvovirus B19 viral protein-induced antibodies against self-antigens like cardiolipin, single-stranded DNA, keratin, and collagen type II, 2. the clinical similarities between parvovirus B19 infection and certain autoimmune diseases like SLE, and 3. the high prevalence of parvovirus B19 DNA as well as positive parvovirus B19 serological tests in patients with autoimmune diseases. Nevertheless, the exact pathogenetic mechanisms behind this relation remains unclear. In this regard, Esrigun presented 3 proposed mechanisms for evoking the immune system to produce autoimmune phenomena namely, molecular mimicry, self-antigen presenting to T cells brought on by erythroblast apoptosis triggered by parvovirus B19, and phospholipase activity of the particular area of parvovirus B19 VP1 protein. Autoimmune diseases caused by similar mechanisms, such as SLE, autoimmune-mediated heart diseases like myocarditis and dilated cardiomyopathy, as well as autoimmune hemolytic anemia were discussed. Unsurprisingly, a recent study showed that parvovirus is associated with autoimmune thyroiditis [196].

Kiyak and colleagues introduced the role of ferritin in the autoimmune as well as inflammatory process until its recent role in the patients with severe COVID-19. The study served as a base for the extensive pathogenetic role ferritin has played and still in various pathological processes [56]. Later on, the central and critical role played by ferritin

from hyperferritinemia to COVID-19 was discussed by Alrais and colleagues. Ferritin is more than just a measure of the body iron levels, indeed. For instance, ferritin, which is also referred to as an acute phase reactant, is often raised in a number of infections as well as inflammatory and autoimmune illnesses [56]. In fact, the term "hyperferritinemic syndrome" has been used to refer to four disorders where ferritin is a major pillar, adult-onset Still's disease (AOSD), catastrophic antiphospholipid syndrome (cAPS), macrophage activation syndrome (MAS), and septic shock. Nevertheless, COVID-19 was shown to be a justified candidate for being the 5th member among the disorders listed under hyperferritinemic syndrome. The association between significantly raised ferritin levels and COVID-19 severity and consequently the high mortality in these patients rate was highlighted as a base for the new membership [197].

Ilan and friends argued about whether 3-month period of Cognitive Behavioral and Mindfulness-Based Stress Reduction (COBMINDEX), which improved the wellbeing and inflammatory state of Crohn's disease (CD) patients, may also affect the gut microbiome. The COBMINDEX intervention, according to the results, showed a considerable impact on microbial diversity and its relationship to the inflammatory profile of CD patients. The associations between variations in the abundances of taxa unrelated to CD and inflammatory indicators suggests potential microbial targets in CD. Therefore, the authors concluded that COBMINDEX has improved patients quality of life and reduced psychiatric symptoms and fatigue. Actually, patients with severe early psychological symptoms most benefited from COBMINDEX [198].

An update on HIV and autoimmunity was presented by Tocut. The range of documented autoimmune manifestations in HIV-infected individuals receiving antiretroviral treatment (ART) is indeed expanding. With the introduction of ART, rheumatic symptoms related to early HIV infection have diminished, but the prevalence of autoimmune disorders, mainly due to immune reconstitution inflammatory syndrome (IRIS) have grown [199]. Through an extensive review of medical literature published from 2002 to 2021 regarding HIV infection and autoimmunity, various autoimmune disorders were documented including vasculitis, immune cytopenias, rheumatic diseases, SLE, APS, sarcoidosis, and thyroid diseases, among others [200,201].

In regard to COVID-19 and autoimmunity, Adiguzel showed that unlike the SARS-CoV-2 infection, the omicron variant 21K infection may cause autoimmune phenomena in people with the HLA-A*24:02 and HLA-B*15:01 alleles, whereas omicron 21L infection may be associated with autoimmunity in individuals with HLA-A*24:02 allele. Nevertheless, experimental research is still needed to validate these results.

The association of metabolites with infectious and autoimmune diseases was presented by Tsoukalas. While autoimmune diseases (ADs) are the most common chronic inflammatory conditions characterized by the loss of self-tolerance, affecting 5–10% of the global population; metabolic complications and micronutrient deficiencies caused by dietary and lifestyle factors are common features of ADs. Targeting metabolic perturbations has emerged as promising approach in disease diagnosis and discovery of novel therapeutic targets. The advantage of this strategy is its ability to capture subtle but significant changes that drive disease pathogenesis as metabolic pressure presents before symptoms occur. For instance, insulin resistance, changes in the gut microbiota, weak antioxidant defenses, and decreased exposure to physiological germs—a process required for immune system maturation- are all examples of metabolic imbalances that contribute to immune function dysregulation. Furthermore, the identification of biomarkers using metabolomics has demonstrated a potential to improve clinical outcomes in patients with ADs by restoring nutritional shortages and reversing the metabolic state [202]. Similarly, new developments in studying ADs such as RA, SLE, and multiple sclerosis using metabolomics was reported recently [203].

10. Novelties in autoimmunity during AUTO13

Mucous membrane pemphigoid (MMP) is a rare autoimmune disorder of the mucous membranes, including the oral cavity, conjunctivae, skin, genitalia, anus, and to a lesser degree the nasopharynx, esophagus, and larynx [204]. While upper airway involvement is known; lower airway involvement has not been described. Therefore, A. Razzaque and colleagues proposed a new disease entity called "pulmonary pemphigoid". In an extensive literature search a total of 11 patients with MMP involving the lower airways were found. At median age of 20, the mortality rate was 45%. Therefore, early diagnosis and management would definitely lead to a better outcome. The findings presented by the authors were supported by several articles in the medical literature [205–207].

While non-caseating granulomas occur in different organs but most commonly in the lungs, eye involvement is well documented in sarcoidosis [208]; the cause of uveitis in sarcoidosis is not known. Schrijver and friends investigated whether autoimmunity plays a role in the development of uveitis in sarcoidosis. Out of 91 sarcoidosis patients, 46 had uveitis with significantly higher serum anti-retinal antibodies (ARA). The association between serum ARA and sarcoid uveitis has not been reported before. This finding was supported by a correlation between sarcoid uveitis and specific TCR/BCR clonotypes. Actually, in a study concerning the presence of ARA, sarcoidosis was found among the enrollees [209].

Koneczny and colleagues suggested that IgG4 autoimmune disease (IgG4-AID) and IgG4 related disease (IgG4-RLD) are distinct diseases. IgG4-RLD is a fibro-inflammatory disease causing multiple organ swelling and elevated levels of serum IgG4 [210]. In turn, IgG4-AID which is characterized by autoantibodies of IgG4 class, is a new emerging disease with antigens found throughout the body particularly in 4 distinct locations: the peripheral nervous system, skin, kidneys and blood circulation, accompanied most predominantly by anti-neural IgG4-AID [211]. By studying 50 anti-neuronal IgG4-AID and 19 IgG4-RLD patients, the authors found that patients with IgG4-RLD had higher IgG4 serum concentration than in IgG4-AID. In the latter, though IgG4 were elevated, patients did not fulfil the criteria for IgG4-RLD and the autoantibodies titers did not correspond to the IgG4 serum concentrations. Moreover, patients with IgG4-RLD did not have anti-neuronal/muscular IgG4 autoantibodies, and IgG4-RLD male patients had more frequently elevated levels of serum IgG4 compared to females [212].

The effectiveness of a gluten-free diet (GFD) in autoimmune diseases (ADs) was presented by Lerner, concluding 83 papers in which GFD was used to treat 29 ADs. Rheumatic, skin, muscular, connective tissue, intestinal, hepatic and biliary, thyroidal, adrenal, hematological, cardiac, kidney, ophthalmic, gynecological, and cerebral illnesses were all discussed. Gluten withdrawal was effective in roughly 80% of the tested ADs, according to the findings which might be the start of a novel dietary therapy for autoimmunity [213].

Seida R. discussed the immunomodulatory effects of CBD by presenting a patient with severe psoriatic arthritis manifested by painful arthritis in her knees, ankles, and hand joints. Multiple drug regimens were used including DMARDs, TNF-alpha inhibitors, anti-IL-17, ustekinumab, and JAK inhibitors. However, none had brought any improvement. Upadicitinib, a JAK inhibitor, was the only drug with partial clinical response. Due to severe pain, the patient was then treated with CBD, which surprisingly resulted in a complete skin and join remission. The mechanisms in which cannabinoids may contribute to an anti-inflammatory and immunomodulatory role via multiple receptors, mainly CB1R and CB2R, as well as GPR55 and adenosine a2a receptors, were discussed by Seida R. This suggests that cannabinoids can be an effective adjunct show anti-inflammatory properties. Interestingly, a study conducted on patients with psoriatic arthritis found that IL-23 levels were significantly higher in cannabis non-users than in users [214].

Vadasz elucidated new signaling pathway, CD72- CD6 axis on activated CD4+ T cells. Increased amount of CD72 has been detected in autoimmune diseases, however, CD6 receptor was a candidate for proinflammatory pathway in CD4+ T cells for this ligand [215]. Analysis on peripheral blood mononuclear cells taken from 15 healthy individuals showed that CD72 has significant effect on proinflammatory cytokines, such as IL-17 and IFN-γ. Therefore, the presenter concluded that targeting this novel axis and CD72 might become handy in the future for the treatment of autoimmune diseases [216].

11. Conclusion

Due to their importance and relevance, the topics presented during AUTO13 were numerous and various, as illustrated. Though great efforts were made to bring as many updates as possible, yet not all the abstracts were included. Nevertheless, as the field of autoimmunity keeps fascinating and attracts more research, the mission of concluding autoimmunity meetings will inevitably become harder. Attending such gatherings, particularly in person, is a great opportunity to contribute to this important field.

Declaration of Competing Interest

The authors declare no competing interests.

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