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Autoimmunity Reviews 20 (2021) 102945

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Review

The mosaic of autoimmunity - A taste for more. The 12th international congress of autoimmunity 2021 (AUTO12) virtual

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ARTICLE INFO

Keywords:
Autoimmunity
Autoantibodies
SARS-CoV-2
COVID-19
HLA
AUTO*12*

ABSTRACT

Notwithstanding the fact that the 12th international congress of autoimmunity (AUTO12) was held virtual this year, the number of the abstracts submitted and those presented crossed the thousand marks. Leading investigators and researchers from all over the world presented the latest developments of their research in the domain of autoimmunity and its correlation with various diseases. In terms of mechanisms of autoimmunity, an update on the mechanisms behind the association of autoimmunity with systemic diseases focusing on hyperstimulation was presented during AUTO12. In addition, a new mechanism of ASIA syndrome caused by an intrauterine contraceptive device was revealed demonstrating a complete resolution of symptoms following device removal. In regard to the correlation between autoimmunity and neurogenerative diseases, the loss of structural protein integrity as the trigger of immunological response was shown. Schizophrenia as well, and its correlation to pro-inflammatory cytokines was also addressed. Furthermore, and as it was said AUTO12 virtual due to COVID-19 pandemic, various works were dedicated to SARS-CoV-2 infection and COVID-19 in terms of autoimmune mechanisms involved in the pathogenesis, treatment and complications of COVID-19. For instance, the correlation between autoimmunity and the severity of COVID-19 was viewed. Moreover, the presence and association of autoantibodies in COVID-19 was also demonstrated, as well as the clinical outcomes of COVID-19 in patients with rheumatic diseases. Finally, immune-mediated reactions and processes secondary to SARS-CoV-2 vaccination was displayed. Due to the immense importance of all of the topics addressed and while several hundreds of works were presented which cannot be summed up in one paper, we aimed hereby to highlight some of the outstanding abstracts and presentations during AUTO12.

1. Introduction

Autoimmunity has served for decades as the connecting base for etiologic and pathogenetic processes of numerous systemic diseases [1–3]. Serving as the first line of defense against invasion, various triggers have been described to dysregulate the immune response causing autoimmune diseases [4]. The triggers of such dysregulated response were shown to be foreign bodies [5], infectious agents [6], chemical or pollution triggers [7] among others. The large base of the connection between autoimmunity and clinical diseases raised the need for a concise gathering of leading experts in the domain of autoimmunity and its branches of clinical immunology, allergy, and rheumatic diseases. Therefore, prof. Shoenfeld was the initiator and leader of organizing an annual meeting under the title of "international congress of autoimmunity" abbreviated as "AUTO" more than a decade ago. The need for such gathering was even greater during the pandemic of COVID-19 since SARS-CoV-2 infection was associated with many immune and autoimmune mechanisms contributing both for morbidity and mortality [8,9], in addition to the role immune-modulators and immunosuppressants have played in the management of patients with COVID-

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https://doi.org/10.1016/j.autrev.2021.102945
Received 22 June 2021; Accepted 29 June 2021
Available online 9 September 2021

19, particularly in severe disease [10,11]. However, and due to the restrictions of the COVID-19 pandemic, the 12th international congress of autoimmunity (AUTO12) was held virtual this year. Hundreds of abstracts were submitted both for the oral and poster presentation and approximately 500 abstracts were accepted for the congress in all of its sessions. COVID-19 as mentioned, though restricted the physical gathering, constituted a large part of the discussions during the congress. Leading researchers and physicians from more than 40 countries presented in the plenary, parallel and poster sessions. Seeking to spread the knowledge of this important domain for as many colleagues and researchers as possible, we brought here on the tip of the fork some of the lectures presented during AUTO12. As the presentations reached over 500, only a small part was summed up thus called "a taste for more". An updated medical literature was cited accordingly.

2. Virtual meeting pros and cons, the example of AUTO12 by Jan Damoiseaux

The 12th International Congress on Autoimmunity (AUTO12) was originally scheduled for May 2020, but was, due to the SARS-CoV-2 pandemic, first postponed to November 2020 and then to May 2021. However, in the beginning of 2021, it became apparent that a live event was not an option, neither was further postponement. Therefore, it was decided to organize an on-line event with full attention for scientific sessions, poster exhibitions, as well as sponsors. In the virtual conference center participants were introduced to easily find their topic of interest. The pros and cons of a virtual meeting will be discussed here as a personal reflection.

The schedule of the scientific sessions remained largely in line with the previous AUTO, that is, the conference days started with a plenary session, followed by two or three series of up to seven parallel sessions. All presentations, both of the plenary and parallel sessions, were prerecorded. This was professionally organized by the congress company KENES. Presenters were supported in order to have optimal sound and vision. In case of unwanted disturbances, the recording could be interrupted and continued as required. Although prerecording facilitated optimal programming of the sessions without delay because of better controlling the time allotted to the speaker and the lack of extended discussion, the presenters were not familiar with the content of the preceding lectures in their session of even in the overall congress. As a result, introductions within one and the same session were partially overlapping by referring to the same studies with similar slides. In a live event, presenters most often skip one or two slides if they already have been presented before. Despite some unnecessary repetitions, the on-demand availability of the presentations had several clear advantages. First, presentations could be started in any sequence of interest and, thereby, participants could create their own session by combining presentations with the same topic (for instance multiple sclerosis or mechanisms of intravenous immunoglobulin treatment), but originally scheduled in different sessions. This option, obviously, nullified the disadvantage of repetitions in the introductions as mentioned above. Second, presentations programmed in distinct parallel sessions could be easily attended: no problems with moving to other rooms at the other end of the convention center and experiencing that all seats are occupied or that synchronicity between parallel sessions has been lost. By on-demand availability even simultaneous lectures were accessible in the on-line version. Third, on-line presentations could be stopped and even (partially) repeated. I used this option several times in order to better understand some details or to have a closer look at the data presented on the slide. During a live-event participants increasingly tend to make pictures of interesting slides, which on the one hand may be somewhat disturbing for participants sitting around, but on the other hand raises some ethical concerns with respect to unwanted distribution of unpublished data. The latter is, of course, not prevented by an on-line congress, but presenters often added a remark at the bottom of their slides, like "unpublished data; do not distribute". Irrespective of attending a live or on-line scientific event, the idea is to share data and to discuss the implications of these data. We have to rely on good ethical behavior in science, otherwise only published data will be presented at scientific meetings. This would make the meetings less interesting for participants and would hamper steady progression in the scientific area of interest. Unfortunately, the AUTO12 also entailed multiple presentations that already had been published in international journals. However, this was primarily due to the postponements of the meeting because many participants already submitted their abstracts more than one year before the eventual on-line meeting.

The overall feeling of enthusiasm after having attended AUTO12 depends on the amount of novel information that has been acquired and potentially can be incorporated in the personal network knowledge of the (auto-)immune system or in the ongoing activities of the research team one is involved. In live events one tends to remain in the same parallel session for the reasons already elaborated upon. As such, presentations that at first sight might seem less interesting, may greatly surprise. Because of limited experience with on-line meetings, I had a tendency to select primarily overview presentations of renowned colleagues instead of giving attention to presentations of the young scientists or even *E*-posters. The on-line presentations, however, could be attended in a private environment that, depending on the level of background noise and stable internet facilities, enabled a more concentrated attention for the content. Facilities to make notes were better than in an average convention hall in terms of space available on the working desk. Furthermore, coffee and lunch breaks, or even outdoor workouts, could be incorporated as personally required. This enabled me to expand the daily timespan that I could follow the presentations which was reflected in the enormous number of notes that I have made during the three main days of the AUTO12. The prolonged availability of the on-demand lectures, obviously, also enables to spread the activities over a longer time, but personally I preferred to have the best "congress mood" by mimicking a live event as close as possible. After "returning" from an intense meeting, like AUTO12 can be, daily professional life tends to take over very rapidly and prevents from further congress participation.

Talking about "returning" inevitably is linked with the world-wide traveling which is required for attending live events. Besides being an environmental challenge in terms of the climate change, it also has an impact on personal fitness, especially for those coming from another time-zone. In addition, traveling is time consuming and may be an organizational challenge for family life. On the other hand, live events are often organized in cities with a great history. This enables participants to have a sneak preview of the pearls of, for instance, Granada, Lisbon or Athens. The latter was the intended site for the AUTO12, but, luckily, the organization has decided to have the AUTO13 next year (2022) in Athens.

In the end there are many pros of an on-line meeting. When asking the participants, many more advantages will probably be mentioned, but there was substantial lack of one of the most important ingredients of a scientific meeting, which is social interaction. Over the years, the people working in the field of autoimmunity and attending the previous AUTO meetings have become sort of a family. In particular after more than one year of different degrees of lock-down, there is growing need to experience that our friends are still doing well. Besides social interaction, also scientific discussion is propelling the field forward in the benefit of patients with autoimmune diseases. The on-demand availability largely prevented from lively discussions and exchange of ideas, eventually resulting in effective collaborations. Therefore, I sincerely hope that the AUTO13 will be a live event!

3. Topics discussed during AUTO12

3.1. Mechanisms of autoimmunity during AUTO12

Prof. Yehuda Shoenfeld illustrated the mechanisms behind

developing autoimmune diseases, starting from hyperstimulation or triggering of the immune system. The mechanisms include genetic predisposition, use of adjuvants such as vaccines, foreign bodies or material as silicone, infections, estrogen, prolactin and checkpoint inhibitors among others.

Genetic factors are numerous, for instance polymorphism of HLA-DRB1 was shown to be associated with the development of autoimmune diseases [12]. Moreover, patients of European descent who were treated with immune checkpoint inhibitors and developed inflammatory arthritis, were more likely to have at least one shared epitope allele of HLA-DRB1 than healthy controls [13]. On the other hand, the classical allele HLA-DRB1*04:05 is believed to be a major contributor to resistance against enteric fever [14].

In turn, women with silicone breast implants (SBIs) have a higher chance of rheumatic or autoimmune disorder diagnosis. In a cross-sectional study conducted by Watad et al. [15] including 24,651 SBI recipients and 98,604 matched SBI-free women, the strongest association with SBIs was noted for Sjogren's syndrome, systemic sclerosis (SSc) and sarcoidosis (OR of 1.58, 1.63 and 1.98, respectively). In fact, the association between autoimmune diseases and SBIs is part of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) which was described for the first time by Shoenfeld [16]. Genetic as well as other materials like aluminium (adjuvants) play a major role in the etiology of ASIA Syndrome. The manifestations of ASIA syndrome include myalgia, chronic fatigue, sleep disturbances, cognitive impairment and memory loss. In addition, an association between SBIs and lymphoma, mainly of non-Hodgkin subtype has been previously described [17,18].

De Rosa highlighted the key-role of the discovery of the transcription factor Forkhead box-p3 (Foxp3) for understanding the molecular determinants leading to generation and maintenance of T regulatory (Treg) cells. In fact, previous studies showed that precise transcriptional and epigenetic events are needed to guarantee a stable expression of Foxp3 in Treg cells [19,20]. De Rosa et al. assumed in their current study that specific modifications of DNA and histones are essential for the establishment of the chromatin structure in conventional $CD4^{+}$ T (Tconv) cells for their future differentiation into the Treg cell lineage. Early oscillatory changes in Foxp3 were noted during these events [21]. The authors concluded that better understanding of the transcriptional and epigenetic determinants correlated to Foxp3 gene expression and transcription aids in the configuration of the gentle balance between immune tolerance and autoimmunity as pointed before in medical literature [22,23].

In a study including peripheral blood mononuclear cells (PBMCs) from 30 patients with SLE, 25 patients with RA, and 70 healthy controls (HC), Pappa et al. demonstrated that an increased DNA damage is present among systemic autoimmune diseases patients compared to a control group. A more condensed chromatin organization and defective global genome repair could also be observed in patients with autoimmune diseases. in fact, DNA damage and accumulation could contribute for systemic autoimmune diseases [24].

Lovsin et al. analyzed a whole epigenome of patients with periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) using pooled DNA libraries enriched for methylated genomic regions and identified candidate genes. The authors found that PIK3AP1 and SPON2 intronic gene regions are differentially methylated in patients with PFAPA, which could serve as an indication that B cell adapter protein (BCAP), such as PI3K binding inhibitor of inflammation and spondin-2 (SPON2), could be a major factor in the etiology of PFAPA [25].

Intending to figure out whether polymorphism of HLA gene locus, particularly HLA-DRB1, is associated with IgG4 autoimmune diseases (IgG4-AID) [26], Koneczny et al. performed a systematic review and meta-analysis which included case-control studies on genetic association of class I IgG4 autoimmune diseases. The authors showed that patients with IgG4-autoimmune diseases have significantly increased frequency of HLA-DRB1*14, HLA-DQB1*05 and the HLA-DRB1*14-DQB1*05 haplotype and a decreased frequency of HLA-DRB1*13. Therefore, it was assumed that HLA-DRB1*14 and DQB1*05 allele could increase the chances of developing IgG4 autoimmune disease, while HLA-DRB1*13 may have a protective effect. The findings were previously described by the Koneczny and colleagues [27].

Tanay presented the link between allergy and autoimmunity as they are both a consequence of a dysregulated immune system. Epidemiological studies show that allergies and autoimmune diseases increase simultaneously. In addition, allergic and autoimmune diseases share several aspects in common, such as: IgE genes autoreactivity, cytokines, mast cell involvement, T regulatory cells (Treg). Other similarities include shared genetic susceptibility loci and commonalities in the pathways between allergy and autoimmune processes. Moreover, in terms of cytokines, IL-17 seems to play a role in the development of allergic diseases as well as autoimmune diseases. Several papers were published before supporting the shared mechanisms of allergy and autoimmune diseases [4,28–30].

The pro-inflammatory IL-33, from the IL-1 family, has shown to be elevated in previous studies on inflammatory arthritis, such as rheumatoid arthritis (RA) [31] and ankylosing spondylitis (AS) [32]. In addition, it was found that IL-33 plays a pathogenetic role in Sjogren's syndrome [33]. Abou-Raya et al. investigated the role of IL-33 in patients with RA, including correlation of its serum markers with disease activity and clinical manifestations. A total of 60 RA patients and 40 healthy controls were selected for the study. The levels of IL-33 were significantly elevated in patients with RA and correlated with disease activity, including laboratory manifestations such as DAS28, ESR, CRP, rheumatoid factor, anti-CCP, TNF-α, and IL-6. Furthermore, IL-33 showed a dramatic decline in patients treated with anti-TNF-α or anti-IL-6. IL-33, the authors concluded seems to have a critical role in the pathogenesis and clinical activity of RA and could be a potential target of treatment. The correlation of IL-33 with treatment targets was mentioned by Verri et al. [34]. In addition,

As adjuvants, which are found in vaccines, are well described of inducing autoimmune diseases in the form of ASIA syndrome [35] an interesting work by Cohen et al. presented the development of ASIA syndrome among 34 female patients who underwent Essure sterilization device removal secondary to various complaints presented by percentage as 41% reported severe fatigue, 62% reported myalgias and/or arthralgias, 32% reported cognitive impairment, 50% developed inflammatory bowel syndrome, 29% developed hair loss, and 6% had a new diagnosis of inflammatory bowel syndrome. Removal of the device resulted in the resolution of almost all symptoms. The author concluded that Essure device sterilization might result in symptoms associated with foreign body induced ASIA, assuming that Polyethylene Teraphalate and Nickel/Titanium alloy coil, which both presented in the Essure device, may be responsible for this phenomenon. The authors described related data in the past regarding foreign bodies implantation such as silicone in breast implants [36] and polypropylene mesh in hernia or pelvic organ prolapse repairs [37]. Furthermore, in a recent study, Cohen et al. stated that pre-existent allergic disease found to be an important risk factor for the development of ASIA after foreign body implantation [38].

The pro-inflammatory imbalance which results in renal diseases is poorly understood, as was highlighted by Chebotareva et al. The authors pointed to the unclear pathogenesis of chronic glomerulonephritis (CGN) with nephrotic syndrome (NS) and aimed to assess the clinical significance of the Th17, Th1, and Treg cytokines in relation to the activity and progression of CGN. The study included 98 patients with CGN while comparing laboratory data to the healthy population and patients with CGN without nephrotic syndrome. The results demonstrated an imbalance between the proinflammatory cytokines (TNF-α, IL-6 and IL-17A) and anti-inflammatory factors (IL-10 and Treg in the tissue) which was most pronounced in CGN with NS. Additionally, a decrease in the regulatory anti-inflammatory link (Treg) in the kidney tissue was observed in FSGS, the most severe form of CGN. The results point to the role of immune cells and cytokines in the pathogenesis of CGN and thus

open possibilities for management. The role of proinflammatory cytokines in different glomerulonephritides was similarly demonstrated by Stangou et al. [39]. In their study, urinary excretion of cytokines was correlated to histological data attained by a kidney biopsy and compared to renal function outcomes in both focal segmental necrotizing glomerulonephritis (FSNGN) and IgA nephropathy. Their results demonstrated a differing role of pro-inflammatory cytokines in the progression of these diseases; Th1 and Th2 cytokines being more strongly implicated in the pathogenesis of IgA nephropathy while their effect was mediated by MCP-1 production in FSNGN. Furthermore, IL-17 and IL-6 production was linked, in both conditions, to the stimulation of renal inflammation and development of renal injury, respectively; Prompting further studies to explore new treatment options. IL-17 and TH17 cells were also found to be associated with other renal inflammatory conditions, as was demonstrated by Dolff et al. [40]. It was demonstrated in their review that TH17 cells, through the secretion of pro-inflammatory cytokines such as IL-17A, drive renal autoimmunity by stimulating autoantibody formation, as well as fuelling tissue inflammation; thereby leading to the pathogenesis of many autoimmune diseases with renal involvement.

The role of immune cells in renal diseases were further explored by Appelgren et al. In their case-control study, B-cells from granulomatosis with polyangiitis (GPA) patients were found to effectively regulate T-cell proliferation and IL-17a production but failed to regulate IFN-γ production. The study included 37 GPA patients (22 remission and 15 active) and 31 healthy controls that were analyzed for their B-cell phenotypes. The authors found a profound inability of patient B-cells to regulate T-cell IFN-γ production compared to the healthy controls and suggest this as the possible mechanism by which persistent inflammation leads to the chronic relapsing nature of the disease. These results were corroborated by von Borstel et al. [41]. In their study, B cell population profiles from 85 GPA patients were evaluated and assessed against relapse-free survival in both blood, urine and histology samples. Their results demonstrated that the increased frequency of certain B cells during remission, namely $CD27^{+}$ and $CD28^{hi}$, were linked to a higher risk of disease relapse. Furthermore, it was revealed that these B cell subgroups tended to decrease in frequency in blood samples but increase in frequency in urine and renal biopsy samples close to relapse, implicating their migration and inflammatory activity in GPA disease deterioration and suggesting B cell targeting as possible future treatment for the condition.

A review by Roccatello demonstrated the possible role of B cells in other rheumatic diseases with renal involvement by exploring B cell depletion therapy as a measure for their management. Rituximab, along with anti-CD20 agents and anti-BAFF targeted therapy, proved to be effective in the management of lupus nephritis, steroid dependent and new onset adult minimal change disease (MCD), ANCA associated vasculitis, severe IgA vasculitis, severe cryoglobulinemia and membranous nephropathy; thereby suggesting that suppression of B cells could inhibit T-cells that are considered to be the source of the putative 'permeability factor' causing proteinuria. A review by Santos et al. [42] explored the use of Rituximab in different glomerulopathies. The review demonstrated how the positive effect of Rituximab therapy on diseases like idiopathic membranous nephropathy (IMN), adult minimal-change disease (MCD), pure membranous lupus nephritis and immunoglobulin-mediated membranoproliferative glomerulonephritis (MPGN). However, they advised against Rituximab use in class III/IV lupus nephritis, complement-mediated MPGN and IgA nephropathy. These results therefore support the role of B cells in the pathogenesis of some renal diseases but question their part in the others, implying that renal autoimmunity is not mediated by a single pathologic process but may require independent explorations in relation to different diseases.

While it is agreed that genetics play a role in rheumatic diseases, their exact identity is still largely unknown. Many genome wide association studies (GWAS) have attempted to identify genes that are linked with the disease, such as the study performed by Langefeld et al. [43]. The group used immunochip genotype data from 27,574 individuals in order to identify at-risk alleles that are in association with SLE development, discovering 24 novel SLE-risk regions. However, it is still uncertain how these genes contribute to the pathogenesis of the disease. In his review, Niewold explored how genes set the stage for cytokine responses in SLE, forming the foundation upon which factors like environmental triggers and disease activity then act. Type I interferon drives the inflammatory response in SLE and is highly affected by both autoantibodies and genetic polymorphisms. Specifically, loss of function at PNP, which is most strongly associated with immunodeficiencies, has also been linked with autoimmunity in some cases by stimulating interferon secretion. Additionally, variants of IRF5 were found to be associated with increased levels of IFN-α when present along with SLE specific antibodies.

The role of IRF5 was also explored in a review by Elkon et al. [44] which pointed to its activation in myeloid cells of at-risk healthy individuals as the possible trigger behind SLE pathogenesis. An environmental trigger may then cause activation of B cells and dendritic cells; both cell lines being implicated in the pathogenesis of the disease. It is important to note that the authors also suggested the TLR–SLC15A4-–IRF5 pathway as the cause for the gender bias of SLE, as this pathway is more active in women. The retrospective study by Barnes et al. also supported the role of IRF5 in SLE. In their retrospective study, healthy IRF5-SLE risk haplotype carriers were identified using the Feinstein Genotype and Phenotype (GaP) Registry. It was discovered that risk haplotypes were not associated with IRF5 protein levels, but instead IRF5 hyper-activation in the myeloid compartment leading to formation of autoantibodies such as ANA with anti-Ro and -MPO specificity and increased concentration of circulating plasma cells. This study highlighted the genetic susceptibility of at-risk individuals and how they may be impacted by environmental triggers to develop future autoimmunity.

Epigenetic changes may also contribute to the pathogenesis of autoimmunity, as was explored by Tchorbanov et al. In their case-control study, the PBMC of 10 SLE patients and 10 healthy donors were isolated and cultured in the presence of folic acid, a modulator of gene expression. The results demonstrated how 2 of the SLE patients expressed an increase in the IL-10 producing Breg cells after the incubation with folic acid as opposed to healthy controls. The findings, the authors indicated, could have implications as to future directions of treatment for autoimmunity, as well as a new approach towards the modulation of genetic defects in various rheumatic diseases.

The relationship between inflammation and other pathologic processes in the body, such as atherosclerosis and osteoporosis, was explored in depth by Szekanecz. Common molecular pathways and markers of inflammation were explored and shown to be associated with both cardiovascular disease and fracture risk. Due to the common link, studies exploring the effect of administering drugs targeting one of these conditions to treat the others were explored with varying levels of success. For instance, while bisphosphonates were not shown to improve cardiovascular disease, beta-blockers were shown to block osteoblast inhibition which promoted bone formation. Administering biologics to rheumatic patients was shown to slow the progression of atherosclerosis as well as inhibit angiogenesis factors linked to higher rates of bone resorption. This conclusion was supported in a 3-year prospective study by Chen et al. [45], which explored the bone mineral density (BMD) of patients with rheumatoid arthritis after receiving anti-inflammatory treatment particularly that extra-articular manifestations including cardiovascular are well described in RA [46]. A total of 380 patients with rheumatoid arthritis were recruited between 2014 and 2019 and their BMD was measured at the beginning and end of the trial, during which they received the standard anti-inflammatory treatment for RA. The study demonstrated that biologic treatment had a protective effect against bone loss in the study population as compared to DMRAD therapy alone, which resulted in substantial bone loss. Another paper that explored the relationship suggested by Szekanecz was the meta-analysis conducted by Singh et al. [47] where various studies were

reviewed in an effort to explore the effect of biologics versus synthetic DMRADs on cardiovascular risk in rheumatoid arthritis. The group concluded that biologic anti-inflammatory treatment reduced the risk of major cardiovascular events, with tocilizumab being superior to TNFi and abatacept. Synthetic DMRADs, however, were associated with increased risk of cardiovascular events, leading the authors to advise against their use with regard to reduction of cardiovascular risk.

In their study, Butnaru et al. explored the possibility that neurodegenerative diseases are linked with autoimmunity by exploring the concept that autoimmunity is generated through the modification of self, rather than a reaction against the healthy self. The authors suggested that loss of structural integrity of proteins may lead to an immunologic reaction against them, whether through misrecognition by the immune system or through molecular mimicry leading to activation of B and T cells. A similar perspective was presented in a review by Bonam et al. [48], which explored current evidence suggesting Parkinson's disease (PD) is an autoimmune disease. The article proposed that innate and adaptive immunity dysregulation, specifically against SNCA protein, could drive the pathology of PD. Furthermore, they pointed to various studies who found autoantibodies in the serum of PD patients, which is a hallmark of many autoimmune diseases. This new perspective may have great implications in terms of therapeutic options for diseases currently considered destructive and difficult to control.

Mayorova et al. studied the link between schizophrenia and autoimmunity. In their retrospective study, it was found that schizophrenia risk is associated with increase in proinflammatory cytokines and a decrease in anti-inflammatory ones. Additionally, schizophrenia was found to often occur in patients with a first degree relative with an autoimmune disease; suggesting a further association between the two. While the authors recognize that there are other mechanisms inducing schizophrenia onset, they pointed to autoimmune alterations as a possible contributor in the etiology of schizophrenia. A cohort study by Wang et al. [49] supported this conclusion by assessing the incidence of schizophrenia among patients with autoimmune diseases, as compared to the general population. Their results illustrated a higher risk of subsequent development of schizophrenia among patients with autoimmune diseases, suggesting that autoimmunity could be associated with the pathogenesis of schizophrenia. For instance, neuropsychiatric manifestations of SLE are well described [50].

3.2. COVID-19 and autoimmunity during AUTO12

As the pandemic of COVID-19 is still emerging with hundreds of millions of people affected worldwide, and as SARS-CoV-2 was correlated to various autoimmune processes [51–54], AUTO12 served as the perfect stage for presenting leading works on the topic of COVID-19 and autoimmunity.

Kanduc generally addressed the mechanisms and etiology of autoimmune diseases stating that immunoreactive epitopes derived from SARS-CoV-2 as well as from HCV and HPV viruses composed of peptide sequences which present in human, and once altered or mutated serve as a trigger of cascades of disorders could result eventually inn multiorgan failure. Kanduc emphasized the cross-reactivity as the fundamental mechanism behind the link of infections and autoimmunity which may serve as the platform of effective and safe and effective means of immunotherapies. The interaction between various viral agents and autoimmunity was recently addressed by Vojdani and colleagues as an explanation for the variety of antibodies present simultaneously against several viral pathogens [55]. Redwan et al. reviewed recently the mechanism behind autoimmune disorders in patients with COVID-19 [56].

Adiguzel focused on the pathogenetic mechanisms of SARS-CoV-2 which are related to autoimmunity by obtaining Coronavirus-associated sequences homologous to the specific SARS-CoV-2 peptide. The resulted sequences were matched with human sequences. Eventually, epitope pairs of coronavirus and human sequences were identified. According to the results, the author illustrated an autoimmunity risk in COVID-19 patients with HLA-A*02:01 and HLA-A*24:02 serotypes, through molecular mimicry, which is common to those sourced by other coronaviruses than SARS-CoV-2, and to SARS-CoV-2 as well. The same author addressed in another presentation, the possible molecular mimicry between human and *p. falciparum* homologous to CFLGYFCT-CYFGLFC of SARS-CoV-2 based on that chloroquine derivatives. The findings suggest some benefits in treating COVID-19 patients with chloroquine derivates. The author concluded that immune responses to homologous 10mers with strong binding to HLA-A*24:02 may cause autoimmunity. Nevertheless, the use of chloroquine-based compound in patients with COVID-19 have not shown significant benefit [57,58].

Osman and colleagues investigated the hypothesis that NK dysfunction is the cornerstone for the constellation of cytokine release, organ damage and resultant death. NK dysfunction according to the authors is associated with decrease cytokines needed for NK function such as IL-15, IL-12 and IL-21. Compared with healthy controls, blood samples from patients with severe COVID-19 were analyzed for NK cells (CD45 + CD3-CD56 + CD16+/−), CD56bright/dim subsets, and NK-cell functional activities (surface CD107a (degranulation) and intracellular interferon-γ (IFN-γ)) via flow cytometry. For IL concentration Luminex immunoassays were used. The tests showed significantly reduced level and function of NK alongside IL-12, IL-15 and IL-18. In fact, intense NK activation and trafficking was demonstrated in the early stage of COVID-19 disease [59].

Autoinflammatory dysregulation was also postulated from the early pandemic of COVID-19 to be the initiator of autoimmunity following SARS-CoV-2 infection. Valdivieso Shephard and Nozal correlated the development of autoimmunity with the severity of COVID-19 by studying a total of 60 COVID-19 patients analyzing several variables including in addition to demographic data, inflammatory markers, IL-6, use of tocilizumab, ICU admission and length of hospitalization. The authors came to a conclusion that studies correlating the occurrence of autoimmunity and the clinical outcome in the short and long-term are scarce and further studies are needed to thoroughly investigate this correlation.

In regard to autoimmune serological tests in patients with COVID-19, the following papers were presented. Schiaffino et al. illustrated that screening of autoantibodies in COVID-19 patients may be easily performed by IF on routine rat triple tissue and the presence of the distinct COVID-IF pattern may alert for auto-reactive mediated complications such as thrombotic or neurologic events. Autoantibodies frequency and correlation were reviewed by Gao et al. [60]. Butterweck showed that strong antibody response against SARS Cov-2 nucleoprotein might trigger the formation of antibodies cross-reacting with IL-11, thus impairing immune regulation, triggering cell apoptosis and inhibiting STAT 3 phosphorylation pathway signaling. The author postulated that these antibodies could lead to hyperinflammatory response leading to cytokine storm. Anaya et al. showed that hospitalized patients with COVID-19 exhibit latent rheumatic, thyroid and antiphospholipid autoimmunity which were related to the severity of the disease [61].

On a retrospective cohort study focusing on hyperinflammation and the role of IL inhibitors in patients with COVID-19, Cavalli et al. analyzed the clinical course of the diseases of 392 patients with COVID-19, 62 received anakinra (IL-1 inhibitor), 55 received an IL-6 inhibitors (tocilizumab 29; sarilumab 26), and 275 were not treated by IL inhibitors. At a multivariable analysis, IL-1 inhibition, but not IL-6 inhibition, was associated with a significant reduction of mortality in patients with COVID-19 and hyperinflammation. However, at interaction tests, IL-6 inhibition was effective in a subgroup of patients with markedly high CRP levels, whereas both IL-1 and IL-6 inhibition were more effective in patients with low LDH levels. However, earlier studies showed a decrease in the risk of mortality [62] as well as in-hospital mortality [11] among patients with COVID-19 treated with IL-6 inhibitors.

A systematic review and meta-analysis conducted and presented by a

colleague from Singapore summarized the clinical outcomes of COVID-19 in patients with rheumatic diseases. Hospitalization, oxygen support, ICU admission and death served as the primary outcomes. A total of 1138 patients with rheumatic diseases were included and studied. The analysis demonstrated that patients with rheumatic diseases are vulnerable with high rates of severe outcomes. Geographical variation also noticed as patients from Europe had higher need of oxygen support and had higher mortality rate. Jorge et al. [63] showed recently that the risks of severe COVID-19 outcomes have improved over time in patients with rheumatic diseases but remain high.

3.3. Infections and autoimmunity during AUTO12

In addition to SARS-CoV-2 and COVID-19, several other infectious agents were addressed during the congress.

By a cross-sectional study among 2085 patients with dermatomyositis and polymyositis (DM and PM) treated with various immunosuppressive agents, Mahroum and colleagues found a high risk of viral infections among the patients which varied according to the drug used. Rituximab was shown to poses the greatest risk of viral infections with HBV and parvovirus infections being the most common [64]. Azathioprine and methotrexate were correlated to higher risk of parvovirus B19 infection [65]. The authors recommended for physicians and rheumatologist to review and take into consideration the risk of infection while constructing treatment plan for patients with DM and PM.

During cancer and autoimmunity session, Poole and collaborators demonstrated an increased risk of malignancy in patients with autoimmune diseases following viral infection particularly in patients with SLE and MS. Both SLE and MS patients had increased clinically relevant EBV infection, which was associated with risk for hematological cancers. Vaccination against preventable viral infection is of paramount importance in those patients. A correlation with SLE and malignancy with infectious agents as triggers was described before [66].

Infections were responsible for more than 50% of deaths among SLE patients admitted to the ICU according to Aragon et al. in a retrospective study, a total of 182 patients with SLE with 252 admissions to ICU were analyzed. The main manifestation of the disease was renal involvement however, the leading cause of ICU was an infection. Kedves et al. [67] reported similar findings related to a high risk of infection-related death in patients with SLE.

An interesting association was found by Donatini and Blaye who demonstrated that patients with the combination of nodular thyroiditis, periodontitis, and active oral CMV infection have an increase rate of cancer, overweight or high plasma HA level (tissue destruction marker). The study was conducted over 196 patients consulting a private gastroenterologist-hepatologist-immunologist clinic. The same authors presented a poster showing that positive CMV IgG and high levels of plasma HA are associated with nodular thyroiditis, assuming that previous CMV infection triggered inflammatory cascade while HA might be related to lymphopenia.

Koneczny et al. demonstrated for the first-time severe form of myasthenia gravis as a rare manifestation of acute leptospirosis. The authors isolated a new sequence type of *L. interrogans* as the causative agent [68].

Aiming to determine the factors contributing for the severity and aggressiveness of RA, Kadisa and collaborators studied the correlation between parvovirus B19 (B19V) infection on disease severity. The authors illustrated larger tender joint count in RA patients with active and persistent B19V infection compared to healthy controls. In addition, RA patients with B19V viraemia had higher levels of RF alongside overall aggressiveness of RA. The same applied for levels of TNF-α which found higher in RA patients with active B19V infection. In fact, RA and parvo B19 virus share a long history [69,70].

While the correlation between CMV infection and multiple sclerosis (MS) is highly debated and controversial [71], Efthymiou and colleagues tested the sera of 77 patients with MS first for autoantibodies related to MS and second for IgG antibodies against individual UL57, UL83, UL55, UL44, p38 and UL99 antigens by immunoblotting using whole CMV extract as antigenic substrate. The results demonstrated a high frequency of autoantibodies in patients with anti-CMV antigens. The authors concluded that the presence of MS-related autoantibodies is associated with the presence of antibodies against specific CMV antigens, shedding light on a probable pathogenic role.

3.4. Vaccines and autoimmunity during AUTO12

In AUTO12 several papers were dedicated for the association between vaccines and autoimmune manifestations and diseases.

In 2019, Watad and his colleagues [72] analyzed data from 500 patients with autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA; Shoenfeld's syndrome) syndrome exposed to adjuvants. The mean age was 43.12, with 89% were females. More than 30% of the patients studied had an undefined autoimmune/autoinflammatory reaction diagnosis. The authors demonstrated that polygenic autoimmune diseases such as Undifferentiated Connective Tissue Disease (UCTD) and Sjogren's disease were significantly higher than autoinflammatory diseases (Giant Cell Arthritis, Crohn's disease, Polymyalgia Rheumatica), 92.7% vs. 5.8%, respectively, $p < 0.001$. Furthermore, it was shown that polygenic autoimmune diseases were linked to Hepatitis B vaccine, while polygenic autoinflammatory disorders were associated with the influenza vaccine. In 2021, Watad et al. [73] evaluated immune-mediated disease (IMD) flares or new-onset disease following the novel mRNA/DNA SARS-CoV-2 vaccine. Twenty-seven cases were studied (mean age 54.4 ± 19.2) with a total of 17 flares and 10 new-onset IMD. Around 78% of the cases had at least one underlying autoimmune/rheumatic disease before the vaccination. More than 75% of the cases were mild to moderate in terms of severity, and over 80% responded well to corticosteroid therapy. In both studies, the authors concluded that immune conditions or flares following vaccination are rare, and vaccines benefit outweighs their autoimmune side effects.

Though rare, autoimmune adverse effects of influenza vaccine such as Guillain-Barré syndrome, SLE, RA, MS and pemphigus vulgaris and vasculitis were reported by unclear mechanisms. Borba et al. presented a case report which summarized the association between influenza and cerebral vasculitis, focusing on molecular mimicry. The association between vaccination and autoimmunity was discussed thoroughly before from different aspects [74].

Toplak et al. investigated the safety and immunogenicity of vaccinations, both killed and live attenuated vaccines, in children treated with anti-cytokine therapy. A total of 12 studies were found which included 286 children treated with anti-cytokine therapy at the time of vaccination, by which 7 studies included 150 children who received non-live vaccine and 5 included 136 patients vaccinated with live attenuated vaccine. Most children vaccinated with live attenuated vaccines received booster dose. A decline in immunogenicity compared with healthy controls was observed in some studies. For a conclusion, anti-cytokine therapy was found to have no effect on the safety of vaccination nevertheless, booster doses might be needed. Children treated with immunosuppressive therapy secondary to chronic rheumatic diseases responded as healthy controls when vaccinated against influenza during the 1999–2000 winter season [75]. Inn addition, varicella vaccine in children treated with immunosuppressive therapy for IBD was found tolerable [76].

Romero Castillo and colleagues presented their research field of developing a tolerogenic vaccine against rheumatoid arthritis (RA). Due to the fact that T cells have a major role in the pathogenesis of RA based on the association of RA with certain MHC class II alleles, T cells constitute an important target for therapeutic intervention of RA. The research group aimed to produce the full expression of the human MHC class II molecule in a humanized mice. As the authors have previously shown that modulation of CII-reactive T cells by vaccination with

soluble MHC class II molecules in complex with the glycosylated CII peptide 259–273 efficiently prevents collagen-induced arthritis. Focusing on improving current findings and exploring the mechanisms of the vaccine induce tolerance is the main purpose of the future work of the authors.

3.5. Diagnosis of autoimmune diseases during AUTO12

Standardization and harmonization are two terms that are often intermingled. Standardization refers to the implementation of an officially recognized standard preparation in order to maximize compatibility of results, while harmonization refers to the implementation of guidelines and recommendations to make procedures uniform or mutually compatible. Due to the heterogeneity of the measurant, i.e. polyclonal autoantibodies, standardization is a major challenge, while harmonization may be the best achievable [77]. In this context, the traditional session of the European Autoimmunity Standardization Initiative (EASI) within the International Congress on Autoimmunity focused on the establishment of international standard preparations, the methods for defining cut-offs and the alternative of reporting in likelihood ratio (LR)s. In addition, diagnostic companies were invited to reflect on these issues. Items addressed are expected to contribute to precision health in autoimmune diseases [78].

First, Johan Rönnelid (Uppsala, Sweden) reported on the preparation of a new standard for anti-dsDNA antibodies [79]. Anti-dsDNA antibodies are clinically relevant in the diagnosis and follow-up of systemic lupus erythematosus (SLE). These antibodies are present in about 70% of SLE patients at the time of diagnosis and may predict flares by increased antibody levels [80]. Since the exhaustion of the WHO standard Wo/80 in 2007, candidate material was searched for in a collaborative effort with the European Consensus Finding Study Group (ECFSG). In 2013 a new candidate (15/174) to replace the WHO standard was identified. In a collaborative international study in 36 laboratories the candidate material and 3 independent SLE patient sera were analyzed using different assays for the detection of anti-dsDNA antibodies. Results revealed that, based on the autoantibody levels, different methods did not rank the samples in the same order, indicating that assays most likely detect different types of anti-dsDNA antibodies. However, if data were determined relative to 15/174, variation in results was significantly reduced. It was concluded that it is probably not possible to achieve an optimal standard preparation and, therefore, 15/174 was introduced as reference material. This reagent was also endorsed by the European League Against Rheumatism (EULAR) in 2020.

Test results are often reported as a dichotomous outcome, being either negative or positive. The distinction between both outcomes is bases on the cut-off of the assay used. João Faro Viana (Lisbon, Portugal) elaborated on the different approaches to define the optimal cut-off. The most objective way of defining a cut-off is to choose for the best compromise between sensitivity and specificity. In the ideal situation test results of disease controls do not overlap with test results of the patients with a specific disease. However, in real life there is substantial overlap resulting in false negative and false positive results. By plotting the percentage true positive results (Y-axis; sensitivity) versus the percentage false positive results (X-axis, 1-specificity) for a wide range of cut-off values a receiver operating characteristics (ROC) curve is obtained. The cut-off revealing the point on the curve that is most close to the upper-left corner, where the sum of sensitivity and specificity is the highest, is the best compromise. However, also other strategies can be applied. First, the cut-off can be based on a pre-set specificity (cf 95% or 98%); this enables comparison of assays and, basically, this is applied by using reference values. Alternatively, cut-off values can be based on pre-set sensitivity. Second, the cut-off can be based on likelihood ratios (LR), as will be further elaborated upon in the following paragraphs. Since a LR below 0.1 or above 10 is of a clinically significant value [81], it is also an option to define a grey-zone, revealing equivocal results, based on these LRs. In the end it is important to maximize he proportion of true results, but this depends on the prevalence of the disease in the population that is selected for testing. If the pre-test probability is low, it is better to choose for a cut-off with a high specificity, while in case of a high pre-test probability, sensitivity should be the driver for choosing the cut-off.

The option of defining a grey-zone already includes the need for defining two cut-off values, often referred to as lower-limit of normal and upper-limit of normal. This can be extended to defining cut-offs for test result intervals. With increasing levels of test results, the LR normally increases indicating that high positive results add more value to the appropriate diagnosis than low or medium positive results [81]. This was further elaborated upon in the presentation of Walter Fierz (Bern, Switzerland). Considering that (1) a positive LR is defined as the ratio between true positive and false positive results, and (2) true and false positive results are plotted against each other in an ROC curve, the LR associated with a certain quantitative test result can be deduced from the ROC curve, i.e. the slope of the tangent for that specific test result. If test result values corresponding to the individual points of the curve are available, it is possible to calculate the LRs using the Bézier curves method. This approach is further explained in a recent publication of Fierz and Bossuyt and references therein [82]. According to the new European In Vitro Diagnostic Regulation (EU IVD-R-2017/746) test suppliers should provide extensive data on test characteristics, including LRs, enabling a better judgment of effectiveness, fitness for purpose and efficiency of an autoantibody test. For appropriate implementation, laboratories should report in LRs, clinicians should recognize the advantages, and the added value of LRs should be reimbursed. Evidently, establishment of implementation of LRs in the interpretation of autoantibody test results fits very well within the goals of EASI.

The fourth presentation of Xavier Bossuyt (Leuven, Belgium) included clear cut examples for harmonization of clinical interpretation by the use of LRs. As already published by Van Hoovels et al. immunoassays for rheumatoid factor (RF) vary greatly due to a different cut-off setting [83]. Diagnostic companies either choose for high sensitivity (low cut-off) or high specificity (high cut-off). Since the cut-off is used in the ACR/EULAR classification criteria for rheumatoid arthritis (RA) to define low or high positive, the diversity in cut-off definitions has an strong impact on the classification of RA. The example of anti-neutrophil cytoplasmic antibodies (ANCA) in small vessel vasculitis further illustrates that, while standardization efforts have not yet been successful, harmonization based on LR for test result intervals is very well possible because ROC curves of different ANCA-assays are quite similar [84]. Calculation of LRs appears not restricted to solid-phase immuno-assays, but can also be applied for line/dot blots and indirect immunofluorescence (IIF) assays for anti-nuclear antibodies (ANA) [85,86]. The example of ANA is further detailed in terms of application of the Bézier curves method for calculation of LRs, but for ANA the situation is more complicated because LRs are calculated for a specific diagnosis, while the ANA test is used for multiple diseases. This hampers the definition of a good disease control group for establishing the LRs. More importantly, when comparing automated IIF with solid-phase immuno-assays for ANA, the cut-offs provided by the diagnostic companies are highly different in terms of associated LRs. Again, like for RF in RA, this has consequences for application of ANA testing in disease criteria for SLE [87].

Finally, representatives of 4 diagnostic companies were invited to reflect on the way towards standardization and/or harmonization, with special attention for the policies to define the cut-off for their autoantibody assays. Short presentations were given by Oliver Sendscheid (Euroimmun, Lübeck, Germany), Roger Albesa (Inova/Werfen, San Diego, USA), Dirk Roggenbuck (Medipan/Generic Assays, Berlin, Germany), and Nina Olschowka (ThermoFisher, Freiburg, Germany). In summary, it was recognized that, because a patient produces his/her own set of autoantibodies, standardization is not the way forward. Harmonization initiatives, like the international consensus on ANA patterns (ICAP) [88], the availability of certified reference materials,

and the use of LRs as elaborated on above, are very much appreciated. As a matter of facts, for ANCA testing in small vessel vasculitis a position paper on this topic was signed by representatives of multiple diagnostic companies [89]. With respect to the setting of cut-offs, several items are differentially taken into account. These include ROC curve analyses, the combined presence of autoantibodies, the intended use of the assay, FDA requirements (training set and validation set), upcoming, more rigorous, IVD-R requirements, and also comparison with competitors.

In conclusion, the EASI session on harmonization in autoantibody testing contained multiple items that can be addressed. While several initiatives are already being integrated in current clinical practice, future round table discussions, in the presence of all stakeholders, are required to bring harmonization to the second level.

3.6. Treatment of autoimmune diseases during AUTO12

Carlo Salvarani discussed extensively the treatment of large vessel vasculitis, namely giant cell arteritis (GCA) and Takayasu arteritis (TAK). The issue was long investigated by the authors [90].

Tocilizumab was shown to be effective and to have an indisputable steroid-sparing effect in patients with GCA, unlike TNF-inhibitors, which did not show any beneficial effect in GCA [91].

In regard to TAK, both tocilizumab and anti-TNF showed promising results although the findings were not based on randomized controlled trials [92]. Furthermore, abatacept found to lower the risk of relapses in GCA [93], while it did not have the same effect in TAK [94]. Studies are still running about cytokine signaling dependant on JAK3 and JAK1 in GCA and TAK, nevertheless these are believed to play a major role in a model of chronic inflammation of medium and large arteries. The data on the efficacy of ustekinumab in GCA and TAK is inadequate to determine its impact. A high rate of treatment failure was reported before at 24 weeks when ustekinumab was combined with prednisone [95]. In terms of antiplatelet agents in GCA, the benefit of the use of antiplatelet therapy in order to prevent ischemic complications remains unclear. For instance, Nesher et al. [96] showed that among 175 patients with GCA, only 3 of 36 (8%) of the patients who were treated with aspirin at the time of GCA diagnosis, developed a cranial ischemic complication (CIC) in comparison to 40 out 139 (29%) patients who were not treated with aspirin at the time of diagnosis and developed CIC ($P = 0.01$). The same effect was present when aspirin was initiated after the diagnosis. After 3 months of follow-up, only 3% (2 out of 73) of aspirin-treated patients suffered from CIC, while 13% (12 out of 93) of the patients with GCA who were treated with steroid only had CIC ($p = 0.02$). Similar results were demonstrated by Lee and colleagues [97] who showed that only 16% (11 out of 68) of anti-platelet or anti-coagulant-treated-patients had an ischemic event, compared to 48% (36 out of 75) of patients not receiving such therapy had an ischemic event ($p < 0.0005$). Mortality as well was shown to decrease in patients with GCA treated with low dose aspirin in a study including 145 patients with GCA, particularly in the first two years after diagnosis [98]. Nevertheless, a meta-analysis including 6 retrospective studies [99], reported that antiplatelet/anticoagulant therapy at the time of the diagnosis did not decrease significantly the rates of severe ischemic events ($p = 0.33$) however, the study also indicated that initiating antiplatelet/anticoagulant therapy after GCA-diagnosis could have a marginal effect in preventing sever ischemic events ($p = 0.049$). According to the same study, the risk of bleeding was not found higher among GCA patients. Regarding the use of antiplatelet agents in TAK, a retrospective observational study showed that adult patients with TAK who developed ischemic events used less anti-platelets (14.3%) than those who did not develop ischemic events (82.4%), $P < 0.0001$. The findings may indicate a benefit of using antiplatelets among patients with TAK. However, this conclusion should be approved by studies with higher quality such as randomized controlled trials. Indeed, a beneficial role was previously described [100]. In conclusion it is useful to use adjunctive therapy using tocilizumab in selected patients with GCA, especially in refractory or relapsing GCA cases, or GCA cases with high rates of Glucocorticoids (GC) side effects or complications [101]. The same reference of the EULAR indicates that glucocorticoids should be combined with non-biological disease modifying agents in all TAK patients. In cases of steroid-refractory TAK or relapsing disease, adding tocilizumab [102] and TNF- inhibitors [103] to the conventional therapy could be helpful.

In another presentation Regola et al. reported the contribution of using tocilizumab in patients with GCA. In a monocentric study including 32 patients with GCA treated with tocilizumab: 19 patients were treated for more than 52 weeks whereas 13 of them a dose tapering was performed, while in 2 cases tocilizumab was suspended for disease remission. Only two patients relapsed: one during tapering down, and one after tocilizumab discontinuation. Most patients maintained clinical remission with serological and FDG-PET/CT scan improvement with a reduction of concomitant glucocorticoid therapy. The results were published by the author [104] and were supported by a phase II trial published earlier [105].

Ben-Shabat and collaborators addressed the mortality among patients with GCA in a study including 7294 patients with GCA and 33,688 as controls. Patients with GCA had a minor decrease in median survival time (13.1 years) compared to healthy controls (14.4 years). Moreover, patients with GCA were more prone to death in the first two years after diagnosis and ten years after diagnosis. Patients who were diagnosed with GCA before 70 years of age had also higher mortality rates. The findings were published by the group [106].

The therapeutic potential of IL-2 in autoimmune diseases was presented by Abbas et al. based on the fact that regulatory T-cells (Tregs) are more sensitive to IL-2 which functions as a survival factor for maintaining Tregs in the periphery [107]. In addition, IL-2 also promotes Foxp3 and CTLA-4 expression and therefore supports Tregs stability [108]. At earlier stages of researches, high-doses of IL-2 were used to boost immune responses in patients with cancer or HIV infection in combination with antiviral drugs to restore immune competency however, high doses caused numerous toxicities. Years later, clinical trials emerged using low doses of IL-2. The first ones used low-dose IL-2 to treat steroid-resistant chronic Graft vs. Host disease (GVHD) and vasculitis. More recently, clinical trials are ongoing in autoimmune diseases such as type 1 diabetes mellitus, systemic lupus erythematosus, and graft rejection among others.

In a retrospective study conducted by Ahmed and his colleagues, among 12 patients (mean age 68.25 years) with a resistant-to-conventional therapy Bullous pemphigoid, the combination of rituximab and intravenous immunoglobulin (IVIG) as a novel protocol treatment was examined. Complete clinical resolution was observed in a mean of 4.6 months. Two patients only had a recurrence which responded well to additional rituximab course. Patients were followed for a mean of 73.8 months after discontinuation of therapy, and all have remained in clinical, serological, and immunopathological remission without any adverse events. Based on the results, the authors recommended the protocol of rituximab with IVIG for patients with resistant forms of bullous pemphigoid. A previous long follow-up work of the authors addressed resistant Bullous pemphigoid as well [109].

Pishesha et al. proposed a novel strategy for treating various autoimmune diseases established on the utilization of adducts formed between alpaca-derived single-domain antibody fragments (VHHs/nanobodies) and a diverse set of autoantigens. The research group developed VHHs that recognize MHC-II molecules thus targeting all subclasses of antigen-presenting cells (APCs). The authors find that transfusion of a single dose of VHH_{MHCII}-$MOG_{35–55}$ prevented the induction of experimental autoimmune encephalomyelitis in mouse models. In addition, transfusion of VHH_{MHCII}-p31 maintained normal glucose levels in different settings of a mouse model of type 1 diabetes mellitus. The novel strategy presented by the authors may provide a new way of treating a wide range of autoimmune diseases without the traditional immunosuppressive regimens and their detrimental

consequences. Indeed, antigen-specific tolerance, specifically via tolerogenic dendritic cells, a type of APCs, have been researched with promising preclinical results [110,111].

The immunomodulation features of helminths and their possible effect against autoimmune diseases have been known for several years [112,113]. Based on helminths derivatives, Blank and colleagues presented a potential novel therapy to treat autoimmune diseases through a phosporylcholine-tuftsin (TPC) linked to biological activity of helminths. To test their hypothesis, the authors used murine models of autoimmune diseases, such as systemic lupus erythematosus (SLE), collagen-induced arthritis (CIA), dextransulfatsodiumsalt-(DSS)-induced-colitis, experimental-autoimmune-encephalomyelitis (EAE), and ex-vivo human models from patients with GCA and SLE. The results illustrated a significantly decreased secretion of inflammatory cytokines and an increased anti-inflammatory cytokine IL-10, T- and B-regulatory cells in the murine autoimmune models treated with TPC. Moreover, the results were non-inferior to corticosteroids in the murine model of SLE. In the ex-vivo human models, TPC showed similar results in terms of reducing inflammatory cytokines. TPC derived compounds have been long investigated by Blank et al. [114].

The efficacy of eculizumab, a C5 complement protein inhibitor, used for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and generalized myasthenia gravis [115], was assessed in catastrophic antiphospholipid syndrome (CAPS) by Lopez-Benjume and collaborators based on CAPS registry. Twenty-one patients with CAPS out of 563 patients in the CAPS registry (3.7%) were treated with eculizumab 900 mg weekly for four weeks and 1200 mg fortnightly. Among patients treated, 16 (76.1%) recovered, 4 (19%) died, and one (4.7%) did not respond to the treatment. After a median follow-up of 10.7 months, no evidence of recurrences of thrombosis were documented. The authors concluded that eculizumab can be used in addition to the standard treatment of CAPS. The idea of using eculizumab for antiphospholipid syndrome was supported initially based on animal studies [116]. Human use was reported in 2012 in female patients with CAPS in case report with success [117]. Thereafter, several studies have researched this novel pathway with similar successful results [118,119].

As it is well established that both the number and function of regulatory T-cells in patients with remitting-relapsing multiple sclerosis (RRMS) are abnormal [120,121], Bykovskaia and her colleagues investigated the safety and efficacy of transferring expanded ex vivo autologous Tregs (eTregs) in 34 patients with RRMS. A total of 14 patients were injected once with a 300-450 $\times$ 10^6 of eTregs and followed for a period of 24 weeks. Two weeks after the infusion, Tregs levels were elevated, and relapses were reduced by 76%. However, Tregs population slowly declines following 2–3 months. In regard to safety, the patients reported only minor and short-lasting side effects. The authors viewed their findings as a new treatment option for patients with RRMS. The usage of Tregs for treatment of autoimmune diseases have been studied on several animal models and showed promising results in halting the initiation or the development of those diseases [122,123].

Recently, several studies revealed the possible role of autoantibodies other than antiphospholipid antibodies in reproductive failure [124–126]. Relying on those studies and others, Di Natale and colleagues studied the efficacy, safety, and obstetrical outcome of low-dose corticosteroid (10 mg/day) in the first trimester in women with autoimmune reproductive failure. Autoimmune reproductive failure was defined as three or more pregnancy losses in the presence of antinuclear or anti-thyroid autoantibodies. Twelve subjects were enrolled in the study, 4 of them received low-dose corticosteroid during the first trimester. The authors found that none of the patients developed any complications during pregnancy follow-up and eventually all delivered on term, healthy babies with normal APGAR scores. The authors suggested low dose prednisone for patients with recurrent pregnancy loss and antinuclear autoantibodies during the first trimester to promote live and normal birth. Corticosteroids was shown to improve outcome in females with recurrent miscarriages [127]. In fact, there are lack of large-scale clinical trials published in this topic. According to the website "*clinicaltrials.gov*" currently there is a large scale clinical trial consisting of 242 patients on low-dose prednisone treatment in women with recurrent pregnancy loss [128].

The urgent need for steroid-sparing therapies for minimal change disease and focal segmental glomerulosclerosis were highlighted by Kronbichler et al., which raised the issue of steroid dependence or resistance as a common side effect of treatment. The authors pointed to Rituximab, a B cell depleting monoclonal antibody, as a common off-label treatment for these conditions and emphasized the need for large, multicenterstudies and randomized controlled trials to explore treatment efficacy and safety.

Despite the growing knowledge base regarding the pathophysiology of autoimmunity and the new therapeutic targets suggested, there are still some diseases without an effective treatment. In a review by Vitali et al. [129] the reason behind the lack of therapeutic options for primary Sjogern's syndrome was explored, along with possibilities for future research. They concluded that the high variability of primary Sjogern's disease is most likely to blame, as it is unlikely that a single therapy will be effective for every patient. They suggested a need for large data processing that will enable clinicians to better define disease subcategories so that they may address each group individually and tailor treatments that best fit them.

This idea was further explored by Tzioufas in his review of the Harmonicss system. The review also emphasized the great variation of Sjogern syndrome and explained that simple demographic characteristics, including the age and gender, may affect the clinical phenotypes. Harmonicss, a system that provides harmonization that allows multilevel and multi-dimensional comparisons of Sjogern syndrome populations at EU level, was introduced. With this system, physicians first detect disease phenotype, then define the biomarkers of the disease in order to be able to investigate the functional interactions and thereby break patients into therapeutic subgroups. The goal of the system is to eventually improve the approach to precise treatment.

In a similar fashion to primary Sjogern's syndrome, rheumatoid arthritis (RA) is also considered a difficult to control disease. A review by Acosta-Herrera et al. [130] explored how every patient's genetic background may influence their response to anti-inflammatory treatments, as well as the possibility of the existence of rare variants which could explain the heritability of the condition and provide new avenues for management. The authors call for larger studies to explore the use of genetics to dictate management as was later achieved by Szilagyi et al. in a study aimed to use genetic markers to differentiate between good and poor responders to infliximab therapy. In the group's prospective study, 217 bio-naive RA patients with poor response to DMRAD therapy were enrolled and started on biologic treatment, while 250 genes expression was quantified. The authors found that their kit could predict the 6-month therapeutic response to IFX, discriminating between good responders and non-responders; thereby creating a new precision medicine tool with great potential for clinical practice.

Precision medicine is an evolving concept, which may have broad clinical consequences with relation to treatment. This notion was further explored by Moritz et al., which introduced the concept of autoantigenomics, capturing the autoantigen repertoire of patients with inflammatory demyelinating polyneuropathy by broadly testing autoantigens in parallel. The authors suggested the potential of such an endeavour, allowing not only to divide patients into clinical subgroups, but also their potential as prediction models for diagnosis and prognosis. They claim that autoantigenomics will expand our understanding of all autoimmune diseases when compared to a single or panel autoantibody approaches. The possible advantage of such an endeavour with regard to inflammatory demyelinating polyneuropathy was further demonstrated by Koike et al. [131]. The group reviewed the different disease subtypes and how they vary both clinically and with regards to pathogenesis, as well as how different disease subtypes react to treatment. They explored

how some subgroups show a lower response rate to standard therapy, and thereby emphasize the need for tailored therapy for each subgroup in order to optimize clinical outcome.

Another interesting topic of the presentations was a report by Tarasov et al. on the possibility of using drugs at ultra-high dilutions (UHDs). In experimental, both physical and biological studies, it has been found that due to the use of serial dilution technology combined with external rhythmic action (mechanical or electromagnetic), any substance of synthetic or biological origin in the form of a UHD acquires a qualitatively new property – the ability to affect the "target", i.e. the molecules of the initial substance, inside and outside the body, and alter the physical-chemical or biological properties of the initial substance (modifying effect). It has also been shown in experiments that UHDs of antibodies exert the modifying effect on antigens, which is accompanied by changes in the conformation of target molecules and results in the activation of the associated signaling pathways [132,133]. To date, numerous clinical trials have confirmed that the drugs based on UHDs of antibodies are effective in the treatment of autoimmune diseases (for example, type I diabetes mellitus), as well as inflammatory and infectious diseases, disorders of the gastrointestinal tract, central nervous system, and endocrine system.

Medicine is not the only field for applying the modifying effect of UHDs, which can be used in engineering to create modified materials (superconductors, piezoelectric elements, etc.) [134].

During the presentation, it was reported that the sensitivity of modern immunochemical and spectrometric methods is sufficient to determine the modifying effect of UHDs, which allows the control of identity and specific activity of drugs containing UHDs of antibodies.

At the end of the report, a new-generation drug 'Prospekta' was presented, which had been approved in the Russian Federation for the treatment of stroke. It is a UHD of antibodies to the brain-specific S-100 protein, the biological activity of which has been enhanced using a technological method based on the principle of biofeedback. Currently, clinical trials of this drug as a product for the treatment of ADHD, cognitive impairment and vascular dementia are ongoing.

Declaration of Competing Interest

None.

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Update

Autoimmunity Reviews

Volume 21, Issue 4, April 2022, Page

DOI: https://doi.org/10.1016/j.autrev.2022.103039

Autoimmunity Reviews 21 (2022) 103039

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Corrigendum to "The mosaic of autoimmunity - A taste for more. The 12th international congress of autoimmunity 2021 (AUTO12) virtual" [Autoimmunity Reviews, Volume 20 (2021) 102945]

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The authors regret that the authorship list was incorrect on the original article. The corrected list is above.

The authors would like to apologise for any inconvenience caused.

DOI of original article: https://doi.org/10.1016/j.autrev.2021.102945.
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https://doi.org/10.1016/j.autrev.2022.103039

Available online 7 January 2022