The 7th Israel–Italy Meeting: Updates in Rheumatology and Autoimmunity, January 2019 at Tel Hashomer, Israel

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Many scientific meetings are unique in typically being a friendly, collegial event. The Israel–Italian meeting on updates in rheumatology and autoimmunity is one example. When the first meeting was established in 2012, the founders could not have predicted how successful it would become. Since then, a new generation of rheumatologists and autoimmunologists from both countries have maintained this tradition by participating and presenting their new scientific projects and the creation of new collaborations between scientists from both countries. The 7th meeting, which took place at the Sheba Medical Center, Tel Hashomer, in January 2019, proved to be a success. More than 120 scientists and physicians attended this meeting and actively discussed their new innovative studies and projects.

To enable and encourage physicians and rheumatologists from the north of the country to be part of this scientific event, the second day of the meeting was hosted by the Padeh Medical Center, Poriya, near the city of Tiberius, close to the Sea of Galilee.

Science was engaged with the beauty of nature and history with the present, all with the generous hospitality of the Azrieli Faculty of Medicine, Bar Ilan University, Safed, Israel. Our scientific family became bigger and further collaborations were created. Many studies were presented by young rheumatologists from all institutions. Aspects of rheumatic diseases, pathogenesis, and therapeutic approaches were discussed, but only some of the related articles were chosen to be published in this issue of the *Israeli Medical Association Journal* (*IMAJ*).

ASPECTS OF RHEUMATOID ARTHRITIS AND RELATED DISEASES

Rheumatoid arthritis (RA) is frequently associated with many systemic complications, including cardiovascular diseases [1,2]. The prevalence of atherosclerosis in RA was discussed by Adawi and colleagues [3]. Cardiovascular morbidity and mortality was reviewed. Inflammation was considered to be a key mechanistic pathway in the development of atherosclerosis. Active inflammation triggers plaque rupture leading to acute vascular occlusions. Interleukin 1 (IL-1), IL-17, IL-6, and many autoantibodies have been shown to have an active role in NET formation (NETosis) and the development of autoimmune mediated inflammation. In addition, the authors discussed therapeutic approaches in reducing endothelial dysfunction and cardiovascular morbidity [3,4]. The course of rheumatic diseases during pregnancy was discussed by Andreoli and colleagues [5].

Rheumatic diseases commonly affect women of childbearing age, when they are pregnant or during the postpartum period. A common feature is that active maternal disease in the months prior to conception increases the risk of flares during pregnancy. Due to this common characteristic, maternal and fetal health can be optimized if conception is planned when disease is inactive [5,6].

The development of fibrosis in systemic sclerosis is the subject of many studies and yet is poorly understood [7,8]. The complexity of this issue was reviewed by Di Benedetto's group [9]. The authors discussed the possibility that microvascular damage could be the primary event of SSc, and injured endothelial cells and pericytes may transdifferentiate into myofibroblasts, the cells responsible of fibrosis and collagen deposition in the tissue. In this case, the process of myofibroblast generation may link two pivotal events of SSc, microvascular damage, and fibrosis.

Fibromyalgia is continuously discussed as being a syndrome of unknown etiology but one that severely impairs quality of life [10]. Yavne et al. [11] assessed the impact of participation in a floral design course on psychiatric symptoms in a cohort of fibromyalgia patients. The study shows that participation in a floristry course may lead to a significant reduction in pain and improvement in quality of life in those presenting with fibromyalgia. The issue of autoimmunity contributing to amyotrophic lateral sclerosis (ALS) was reviewed by Ralli's groups [12,13] The researchers suggested a role for the innate immune system, which has shown to induce the activation of microglial cells at the sites of neurodegeneration. Several new therapeutic approaches are also reviewed by the authors.

ISSUES OF SYSTEMIC LUPUS ERYTHEMATOSUS

Cross-reactions between Epstein-Bar virus (EBV) and human systemic lupus erythematosus (SLE) autoantigens was assessed. Kanduc [14] analyzed the whole EBV proteome to find peptides that were common to SLE-related proteins. She was able to find that high numbers of EBV hexapeptides are widespread among 34 human SLE autoantigens. The peptide-sharing pattern was

Figure 1. Participants at the 7th Israel–Italy Meeting: Updates in Rheumatology and Autoimmunity, held in Israel. The invited speakers visited the Padeh Medical Center, Poriya, where they attended a seminar at the facility

Figure 2. The presidents of the 7th Israel–Italy Meeting: Updates in Rheumatology and Autoimmunity

mostly concentrated in complement component C4 and IL-10. This finding supports the findings that SLE autoantigens and EBV cross-reactivity are a major mechanism in EBV-associated etiopathogenesis.

SLE and antiphospholipid syndrome (APS), although two different diseases, share many common aspects. Antiphospholipid antibody positivity can be found in up to 40% of SLE patients, among which the full-blown APS is frequent [15]. However, some features of SLE may develop in patients with primary APS, namely skin pathology and autoantibodies considered not to be found in primary APS. The Meroni and Paule groups [16,17] discussed the possibility that APS and SLE are indeed two sides of the same coin. The cause of recurrent pericarditis is largely unknown; however, most causes are considered to be immune-mediated. Recurrent pericarditis is a frequent manifestation in autoimmune diseases such as in SLE. However, idiopathic pericarditis remains the most frequent. Azzielant and Perricone and their colleagues [18,19] discussed the possibility of genetic factors, human leukocyte antigen haplotypes, and other factors being involved in the pathogenesis of recurrent pericarditis.

NAILFOLD CAPILLAROSCOPY IN PATIENTS WITH AUTOIMMUNE DISEASES

Nailfold capillaroscopy (NVC) is the combination of a microscope and a digital videocamera. It is a non-invasive, inexpensive, and reproducible imaging method that allows the evaluation of structural changes in the peripheral microcirculation. NVC is mainly applied in the diagnosis and evaluation of Raynaud's phenomenon (RP) and in the diagnosis of systemic sclerosis (SSc) [20]. Rossi et al. [21] focused on the role of NVC in differentiating idiopathic RP from those with abnormal capillaroscopic changes who have a higher chances of developing connective autoimmune disorders. Many studies have suggested the use of NVC in evaluating other autoimmune diseases, such as SLE, where pathologic patterns of capillaries are reported to be in correlation with disease activity and relevant autoantibodies [22]. Rimar and co-authors [23] applied NVC to evaluate the course and prognosis of patients presenting with systemic vasculitides. Nailfold video capillaroscopy with a standard ×200 magnification has replaced the older technique enabling to digitally capture measure and compare nailfold microvascular changes in real time.

THERAPEUTIC ISSUES IN AUTOIMMUNE DISEASES

Therapeutic options include the use of glucocorticoids, immunosuppressive therapies, and biologicals. Intravenous immunoglobulins (IVIg), and recently the facilitated subcutaneous rout of immunoglobulins (SCIg), remain highly relevant in many immune mediated diseases [24]. Danieli and co-authors [25] described a 61-year-old man with refractory polymyositis in whom steroids and immune-suppressants failed to achieve remission. He was treated with IVIg (2 g/kg per month), which was switched to (fSCIg; 10% immunoglobulin plus recombinant human hyaluronidase). This mode of therapy was shown to be highly beneficial and safe. Dyspnea, muscle strength, and serum creatine kinase levels all improved. Other studies were also supportive of the efficacy of this therapy [26].

Uveitis is an inflammatory disorder of the uveal tract, the middle layer of the eye. It is highly vascularized and pigmented. Inflammation may involve only one anatomical part of the uvea and therefore is called anterior, intermediate, or posterior uveitis [27]. In a comprehensive review, Gamaleo et al. [28] summarized all treatments, including steroids and immune suppressive therapies, as well as established remedies for treating this condition. For each of these therapies, the authors demonstrated the importance of their initiation as early as possible to prevent chronic damage and improve prognosis.

DIAGNOSTIC ISSUES

Serum rheumatoid factors are autoantibodies of different isotypes directed against the Fc fraction of IgG, which is used widely for the diagnosis of rheumatoid arthritis. Being not highly specific it is reported positive in many other autoim-

mune diseases such as in SLE and Sjögren syndrome. Moll and colleagues [29] summarized the status of RF in a wide spectrum of pathologies, namely in chronic hepatitis C infection assuming that chronic antigenic stimulation may induce RF positivity. In addition, they discussed the connection between viruses, autoimmunity, and cancer.

Antinuclear autoantibodies (ANA) are classical diagnostic markers used for many decades for the diagnosis of almost all autoimmune diseases. Despite advances in methodologies introduced to determine ANA, indirect immunofluorescence using human epithelial cell (HEp-2) substrate remains the most common. Sperotto and Paltere and their groups [30-31] presented their experience in using antibodies directed to the dense fine speckled 70 antigen being a frequent pattern when ANA–HEp-2 is tested for the diagnosis of many autoimmune diseases.

At the conclusion of this collaborative meeting, after leaving the beautiful Galilee region of Israel and returning to Sheba Medical Center in Tel Hashomer, participants commented that they looked forward to gathering again at the next Israel–Italy meeting in Brescia, Italy.

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"A consistent thinker is a thoughtless person, because he conforms to a pattern; he repeats phrases and thinks in a groove"

Jiddu Krishnamurti (1895–1986), Indian philosopher, speaker, and writer