The Fourth Israel-Italy Meeting: Updates in Rheumatology and Autoimmunity

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The Israel-Italy Meeting in the fields of rheumatology and autoimmunity has become a tradition. The fourth meeting, organized by Prof. Mauro Galeazzi, took place in the stunningly beautiful city of Siena in September 2015. Scientists from both countries shared their experience and discussed various relevant issues in the above fields. This time young clinicians were dominant, setting the tone of the future and establishing new collaborations between our two countries. This meeting became further proof that medicine can be a bridge of true friendship between all peoples. Of the many issues that were presented and discussed I would like to mention a few.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

SLE is an autoimmune disease with a high degree of variability at onset, implying that early diagnosis is difficult to establish. Early diagnosis enables prompt therapy, thereby preventing organ damage and improving long-term prognosis. In a large cohort of SLE patients Sebastiani and fellow-researchers [1] showed that the most prevalent symptoms at onset were cutaneous, articular and hematological. Relevant serological analyses should be performed as early as possible [2]. During the last decade, much attention has been directed towards a better understanding of regulatory mechanisms in SLE. Failure or absence of some of these regulatory cells/molecules leads to an increase in autoimmunity and is associated with SLE disease severity. Of these molecules, soluble and membrane-bound CD72 was associated with renal damage in SLE. In addition, the role of B regulatory cells and the presence of many subset types in controlling SLE were also mentioned. Attention was also drawn to the role of other factors in the development of SLE. These include viral infections, pollution and some drugs. Low level of vitamin D is one of these factors and was discussed by several scientists at this meeting. Vitamin D is known for its immunosuppressive effects; therefore, when this regulatory element is not sufficient SLE may remain active. The need for vitamin D replacement in SLE is under evaluation and needs to be determined [3]. Finally, the quality of life of SLE patients was given proper attention. The need to deal with anxiety and depression and the understanding of how all this affects the well-being of SLE patients was discussed [4,5].

GENERAL ASPECTS OF AUTOIMMUNE DISEASES

The question of increased risk of serious infections in patients treated with anti-tumor necrosis factor agents as well as other biological drugs such as rituximab and tocilizumab was discussed. Special consideration was given to the risk of tuberculosis and herpes zoster, pointing to the recommendation to screen for these diseases before initiating the above therapies [6].

Autoimmune rheumatic diseases affect mainly young women during their reproductive years. Thus, contraception counseling is required to prevent negative fetal outcomes and exacerbation of disease symptoms. During the past few years, advances in therapies, clarification of risk factors for adverse pregnancy outcome and a multidisciplinary approach have improved obstetric managing, leading to a high likelihood of favorable outcomes [7,8].

Various aspects and presenting symptoms of diseases such as Sjogren's syndrome, polymyositis, vasculitis and sarcoidosis were described by several participants. The presentations vary; for example, cardiac involvement, pericarditis and others. Understanding patients' genetic background and the role of environmental factors such as metals, mercury and silicone implants should be established and better assessed [9,10]. The development of new tools to improve the diagnosis of autoimmune diseases such as Sjogren's syndrome was discussed. One of these is salivary gland ultrasonography, shown to be a promising tool for the diagnosis and prognostic stratification of patients with primary and secondary Sjogren's syndrome [11].

Many studies are undertaken with the aim of updating the criteria for a better disease classification of systemic sclerosis (SSc). SSc diagnosis may be delayed for several years following the onset of Raynaud's phenomenon (RP). RP, antinuclear antibodies positivity and puffy fingers were recently indicated as "red flags" by the VEDOSS* project. The VEDOSS project aims to identify patients in the very early phase of disease and allow the "window of opportunity" before SSc is advanced and in many cases even irreversible [12].

The topic of biotherapies for autoimmune diseases was extensively discussed. Anti-rheumatic biologic therapies, by interfering with the balance between pro-inflammatory T cells and T regulatory cells, have been shown to be highly beneficial. They reestablish immune toler-

*Very Early Diagnosis of Systemic Sclerosis

ance and maintain adequate regulation of immune mediated inflammation [13].

Antiphospholipid antibodies (aPL) have been advocated as potential mediators of unexplained female infertility, but no evidence has yet been provided to support such an association. Given the inflammatory response observed in gene expression analyses of decidual stromal cells treated with aPL, it is suspected that these antibodies might interfere with uterine decidualization, affecting early stages of implantation [14].

Despite the very high benefit-to-risk ratio of vaccines, the fear of negative side effects has discouraged many people from getting vaccinated, resulting in the reemergence of previously controlled diseases such as measles, pertussis and diphtheria. Thus, a review of what adjuvants are and why they are used in vaccines has led some individuals to hold a closed "black box" attitude towards all vaccines. There is a continuous need to be vigilant and to revisit this "black box" to assess the possible risks of the infrequent and delayed adverse events that can arise in genetically susceptible subjects [15].

AUTO-INFLAMMATORY DISEASES AND THERAPY

Auto-inflammatory diseases are a group of well-defined disorders, some of which are genetically well characterized and related to interleukin-1 (IL-1)-mediated inflammation. Among these is familial Mediterranean fever, which has been successfully treated with anti-IL-1 therapies. In recent years other diseases such as gout, recurrent pericarditis, and juvenile arthritis were considered to be auto-inflammatory. Many pathogenic clinical and therapeutic clues seem to support this interpretation, opening the door to novel treatment choices such as IL-1 therapy [16-18].

FISHING FOR GENES IN AUTOIMMUNITY

Autoimmune diseases are classical examples of multifactorial disorders in which a large number of genes interact with environmental factors to form the final phenotype. Today, the most widely used method to identify autoimmunity genes are genome-wide association studies (GWAS), a method based on screening large panels of patients and controls with hundreds of thousands of single nucleotide polymorphisms (SNPs), using microarray-based technology and whole-exome and whole-genome sequencing. Identification of genes contributing to autoimmunity will help us unravel the complex etiology of these disorders, define new biological pathways, and identify novel targets for the development of new therapeutic drugs [19].

WHAT CAN WE LEARN FROM LARGE DATABASES

The increasing use of computerized medical records has led to the availability of the entire population's clinical data for epidemiological research. Analysis of large databases gives us the opportunity to learn the public's behavior regarding medical services and to investigate how medical interventions affect outcomes over time. Interaction between different co-morbidities can also be better understood by large population studies [20].

In conclusion, the fourth Israel-Italy meeting was a superb festival of science, innovation and planned collaborations between clinicians/scientists from both countries. In 2016 the fifth Israel-Italy meeting will be held in Haifa, Israel, when new data will be collected and presented by young scientists together with those who are world renowned. We look forward to it.

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