Conference Scene

The 4th Asian Congress on Autoimmunity

The 4th Asian Congress on Autoimmunity: Meeting Highlights 11–13 September, 2009, Singapore

The 4th Asian Congress on Autoimmunity was held in Suntec City, Singapore from September 11–13, 2009. The congress was addressed by senior investigators in the field of autoimmunity, rheumatology, immunology and diabetology. Yehuda Shoenfeld and his colleagues put together a vibrant scientific program with focus on the pathogenesis, genetics, mechanisms and clinical aspects of the autoimmune diseases and their treatment modalities. Rheumatoid arthritis, systemic lupus erythematosus, Type I diabetes and autoimmune hepatitis were the main diseases that were discussed by the various scientists, not only from Asia but also from other parts of the world.

The 4th Asian Congress on Autoimmunity was recently held in Singapore (11–13 September 2009) with its primary focus on the pathogenesis, genetics, mechanisms and clinical aspects of the autoimmune diseases and their treatment modalities. The main objective was to bring together on one platform the clinicians, immunologists, rheumatologists and experts in other fields of medicine involved in diagnosis, treatment and research of autoimmune diseases. This year, the Congress took place in the historic Suntec City International Convention and Exhibition Centre with over 200 participants from various countries in Asia as well as those from other parts of the world, including France, UK and Australia. Yehuda Shoenfeld (Israel), the Honorary President of the Congress, had an international organizing committee consisting of Pao-Hsui Feng and Kok-Yong Fong from Singapore as Co-Chairmen, and senior physicians drawn from China, Korea, Japan and India as its members.

There were six plenary sessions and an equal number of free communication sessions focused on diagnosis and pathogenesis, autoimmunity mosaic, immune regulation, autoimmunity and associated conditions, experimental therapies and a session bringing out the current state of knowledge. The free communication sessions were run in parallel at two different halls and this provided an opportunity to young investigators to present and showcase their work to the experts. The poster display sessions were well organized during coffee breaks. A special workshop discussed the available diagnostic methods for

autoimmune diseases. Furthermore, two industry-supported, theme-based symposia were organized that focused on the clinical utility of biomarkers in the diagnosis and prognosis of autoimmune diseases and the other on the use of biologicals in the Asian population with particular reference to the Japanese data. The participants each received a copy of the text book '*Diagnostic Criteria in Autoimmune Diseases*' signed personally by Yehuda Shoenfeld.

Plenary sessions

■ 11 September 2009

Diagnostics & pathogenesis

The first day started with the Plenary Session I entitled 'Diagnostics and Pathogenesis' chaired by Fong and K Conard (Germany). The session opened with introduction and opening remarks by the congress Co-Chair Feng and Shunle Chen (Shanghai Medical Center for Rheumatology, China). It included a plenary lecture on 'Antiphospholipid Antibodies: Where Are We Now' by Tatsuya Atsumi (Hokkaido University Graduate School of Medicine, Japan). He presented current status on the understanding of the antiphospholipid syndrome (APS) characterized by thrombosis in the presence of antiphospholipid antibodies (aPL) and pathophysiology of the syndrome. Karsten Konrad (Technical University Dresden, Germany) discussed the role of 'autonitibodies to asialoglycoprotein receptor (ASGPR) measured by a novel ELISA – revival of a disease activity marker in autoimmune hepatitis'. Their group demonstrated a novel solid-phase immunoassay for the detection of anti-ASGPR antibodies to improve

Narinder Mehra[†] & Neeraj Kumar

[†]Author for correspondence:

Department of Transplant Immunology & Immunogenetics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India

Tel.: +91 112 659 4638

Fax: +91 112 658 8663

narin98@hotmail.com

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

autoimmune hepatitis (AIH) diagnostics and monitoring of disease activity. The session also had a presentation by Chak Lau (University of Dundee, UK) who argued that changes observed in the dendritic cell (DC) function in autoimmune diseases including systemic lupus erythematosus (SLE) are characterized by loss of tolerance to self-antigens. In humans, functional abnormalities of DCs have been reported in patients with SLE, the main thrust of which is on the role of plasmacytoid DCs in lupus pathogenesis. Although the precise role of plasmacytoid DCs in the immune system is still unclear, these cells have been shown to polarize T cells through increased production of IFN- α , which is generally considered to be the central cytokine that contributes to SLE development.

The morning plenary session was concluded with a presentation on the 'Role of IL-17 in the Pathogenesis of Rheumatoid Arthritis' by Ho-Youn Kim (The Catholic University of Korea College of Medicine, Republic of Korea). He demonstrated that the differentiation of IL-17-producing T helper cells (Th17), which play a crucial role in induction of rheumatoid arthritis (RA), is suppressed by the activity of FoxP3-positive regulatory T cells (Tregs). He also demonstrated that TGF- β_1 and IL-6 are crucial for promoting Th17 differentiation through expression of RAR-related orphan receptor γ t (ROR γ t). He proposed that signal transducer and activator of transcription (STAT)-3 is a key molecule for the reciprocal development of the differentiation of ROR γ t⁺ Th17 and the induction of FoxP3-positive Tregs. In this regard, the regulation of STAT-3 link molecules may control pathogenic effects of Th17 in RA patients, and provide a new therapeutic target for the treatment of RA.

Mosaic of autoimmunity

The main highlight of the Plenary Session II, 'The Mosaic of Autoimmunity' was a presentation by Shoenfeld, who discussed on the role of infection in autoimmunity. He presented evidence to show how an infection can lead to the development of autoimmune disease (AID) and also trigger an underlying immune process to become overt AID. Various infectious agents (viruses, bacteria and parasites) may inflict autoimmunity and can alter

the clinical manifestations of an AID. Genetic susceptibility of an individual determines the autoimmune response to certain agents. The episodes of infections throughout the life span of an individual affect autoimmunity. Sometimes, infections during childhood may inflict autoimmunity in adulthood. In some cases, vaccines, similarly to infectious agents may also induce AID. Interestingly, infections can sometimes protect from autoimmunity (i.e., the hygiene theory). A certain infectious agent could play a dual role by inducing one AID in an individual, but protecting from another AID within the same individual.

Kok-Yong Fong discussed the immunologic mechanisms in lupus. He suggested that the immune system acts as both a protector of health as well as perpetrator of disease with cytokines playing the role of communication tools, while immunoglobulins function as killer weapons. He stated that the process of apoptosis can initiate and maintain inflammation in SLE. In the disease process, apoptotic cells become secondarily necrotic owing to impaired clearance. T cells have spontaneous increased activation with a reduced threshold of self-antigens. He stated that IFN- α , IFN- γ and IL-17 can cause AID and that the frequency of Tregs decreases in the active state of lupus. Takao Koike (Hokkaido University Graduate School of Medicine, Japan) discussed about the APS and role of aPLs in the disease. These antibodies are a large and heterogeneous family of circulating immunoglobulins that occur in a wide range of infectious and autoimmune diseases. In APS, blood becomes thick and stickier and causes arterial and venous thrombosis. Autoantibodies associated with the APS are directed against phospholipid-binding plasma proteins, such as β_2 -glycoprotein I (β_2 GPI) and prothrombin or phospholipid-protein complexes, expressed on or bound to the surface of vascular endothelial cells, platelets or other cells. In their experience, hypocomplementemia was observed in patients with primary APS which could be attributed to complement activation and consumption rather than decreased complement production. Furthermore, hypocomplementemia was correlated with anticoagulant activity and TNF- α levels. Both the direct effect

of aPLs on monocytes and/or endothelial cells as well as the complement system were suggested to play crucial roles in the pathogenesis of APS.

Shuiping Jiang (Shantou University Medical College, China) discussed the role of Tregs for the therapy of AIDs and induction of transplantation tolerance. Adoptive cell therapy using *ex vivo*-induced and expanded patient-specific CD4⁺CD25⁺ Tregs has emerged as a promising effective individualized medicine for the treatment of inflammatory diseases. He discussed their current efforts on the pursuit of Treg therapy for the treatment of autoimmune diseases and for the induction of transplantation tolerance. He also described that T-cell receptor transduced Tregs with indirect allorecognition mechanism, attenuate rejection manifestation and accumulate in draining lymph nodes and inside the graft suggesting their systemic effect.

Immune regulation

A separate session was devoted to understanding mechanisms of immune regulation in autoimmune diseases. Matthias von Herrath (La Jolla Institute, USA) in his lecture on 'TLR2 Signaling Improves Immune Regulation to Prevent Type I Diabetes' mentioned that natural Tregs show a gradual increase following resolved antiviral immunity and enhanced TGF- β production. He showed that these cells were TLR2-dependent, had tolerogenic function *in vivo* and were able to diminish autoimmunity without hindering antiviral immunity and viral clearance. During ongoing infection, Tregs were diminished and expanded after resolution of infection in a bystander way. He claimed to identify novel mechanisms by which TLR2 promotes immunoregulation and controls autoimmune diabetes in naive or infected hosts.

In the session on the genetic aspects of autoimmune diseases, Narinder Mehra (All India Institute of Medical Sciences, New Delhi, India) gave the lead lecture discussing the 'Comparative Genomics of Disease Associated HLA-DR3 Haplotypes in Type I Diabetes in Asian-Indians as Compared with Caucasians'. He presented evidence to suggest that in comparison with the Caucasians, Asian Indian patients

with Type I diabetes had multiple HLA-DR3-positive haplotypes (predominantly B8-DR3, B50-DR3 and B58-DR3), all of which are disease associated. Of these, while B8-DR3 is equivalent to that observed in European and North American Caucasian patients, B58-DR3 occurs primarily in the Chinese populations. Conversely, B50-DR3 occurs as a 'unique haplotype' in Asian-Indians, not reported in any other population so far. Furthermore, he presented evidence indicating that the Caucasian-specific ancestral haplotype (AH8.1) is rare in the Indian population, replaced by a variant form referred to as AH8.1v. In addition, this population is characterized by a diverse array of other B8-DR3 haplotypes, for example, HLA-A26-B8-DR3 (AH8.2), A24-B8-DR3 (AH8.3), A3-B8-DR3 (AH8.4), A31-B8-DR3 (AH8.5), A2-B8-DR3 (AH8.6), A11-B8-DR3 (AH8.7) and A33-B8-DR3 (AH8.8). Several of which are disease associated. Despite having several differences, these haplotypes in both populations have HLA-DRB1*0301-DQA1*0501-DQB1*0201 suggesting that B8-DR3-DQ2 haplotypes in the Asian-Indian population and Caucasians might have evolved independently from a common ancestor carrying B8-DR3-DQ2 selectively through a series of recombination and mutation events.

Jinhua Lu (National University of Singapore, Singapore) discussed the role of complement, Toll-like receptors (TLRs) and dendritic cells (DCs) in autoimmunity. He demonstrated that the classical pathway also reacts with self-antigens and homozygous deficiency of the complement of the classical pathway is associated with lupus disease. He explained the properties of complement 1q (C1q) in details and suggested that it was produced by macrophages and DCs, while other cytokines are produced mainly by hepatocytes and poured directly into the blood. C1q plays an important role in the phagocytosis of apoptotic cells. Bernard Leung (National University of Singapore, Singapore) discussed the role of cytokines in the development of autoimmunity and also pathogen-driven clinical response of TNF- α . He reported some plausible approaches for the therapy of autoimmune diseases. Of these, reducing Th1 and Th17 responses

could be the best strategy against autoimmunity, and this may be achieved by using anti-TNF- α and anti-IL-6 monoclonal antibodies, respectively. An alternative approach might be an induction of tolerance through expansion of Tregs. Other candidate cytokines for targeting might be IL-17, IL-18 and IL-33. In addition to this, Temy Mok Mo-yin (Queen Mary Hospital, Hong Kong) discussed the role of novel cytokines in SLE. He suggested that Th17 were of major importance as a distinct subset of effector T cells. The frequency of these cells increased in organs involved in human SLE and in murine lupus models. He also reported that the B-cell activating factor (BAFF) occurs in two forms: cell membrane bound and soluble form. Elevated serum BAFF levels have been reported in SLE. Newer strategies employing blocking of IL-17 and/or BAFF have recently been tried in the management of SLE.

■ 12 September 2009

The second day of the congress started with the Plenary Session on Autoimmunity and associated conditions chaired by HY Kim (ROK) and Eiji Matsuura (Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan). The latter in his lecture presented various disease manifestations such as autoimmune vascular inflammation and oxidative stress, which are common in systemic autoimmune diseases, including SLE and APS, and contribute to the oxidative modification of low-density lipoprotein (oxLDL) and oxLDL- β_2 glycoprotein I (β_2 GPI) complex formation. The oxLDL- β_2 GPI complexes were shown to be present not only in atherosclerotic plaques but also in sera of patients with chronic inflammatory and systemic autoimmune diseases associated with atherosclerotic complications, such as SLE, APS and systemic sclerosis, as well as Type II diabetes mellitus, chronic nephritis and acute coronary syndrome.

Zoltán Szekanecz (University of Debrecen Medical and Health Sciences Center, Hungary) reported on the occurrence of malignancies, predominantly lymphoproliferative disorders in systemic inflammatory diseases, such as RA, lupus, scleroderma or dermatomyositis.

He observed that even though inflammatory diseases increase the risk for the development of malignancies, there are controversial reports highlighting causes of the development of the malignancies. Immunosuppressive and cytotoxic drugs used in antirheumatic therapy, such as methotrexate, cyclophosphamide, azathioprine or anti-TNF biologicals, may also lead to the development of such tumors. Tumor-associated antigens may be produced by inflammatory cells and their production may be increased in RA and other autoimmune diseases.

The post-tea session was completely dedicated to the satellite symposium on the use of biologics in Japan and their applications to the Asian population over a 6-year experience. The session started with opening remarks by T Koike (Japan) followed by a presentation by Hisashi Yamanaka (Tokyo Women's Medical University, Japan) on 'Improvement of Outcome Measures in Rheumatoid Arthritis Patients in the Real World – Message From a Japanese Cohort IORRA'. He argued that most of the rheumatologists actually feel that their patients have been getting better; nevertheless, it is not easy to show the benefit of new drugs in daily practice. His group has been able to establish an institute-based cohort of RA patients designated as IORRA since 2000, and this has helped them to analyze various outcome measures of RA patients in the real world. Through biannual collection of data from physicians, patients and the laboratory, they could enroll more than 5000 RA patients. He demonstrated that the clinical condition of patients improved from 2000 to 2003 largely owing to the use of methotrexate. These improvements are even more significant since the introduction of infliximab in 2003 as the first biologics in Japan.

Following this, Tsutomu Takeuchi (Keio University, Japan), and Yoshiya Tanaka (University of Occupational and Environmental Health, Japan) presented their experience on the use and effect of the drug infliximab (a monoclonal antibody against human TNF- α) on the treatment of RA. In his lecture on 'Evidences of Infliximab Treatment for RA in Japan – Reconfirm and Rising Study', Takeuchi presented data for 5000 RA patients who

received infliximab treatment between 2003 and 2005 showing overall acceptable safety profile, risk factors associated with adverse events, and countermeasures for tuberculosis and other type of infections such as pneumonia. Their results raised the possibility that dose adjustment of infliximab could be applied to the daily clinical practice to maximize efficacy of the biologics in Asian countries such as Japan. Y Tanaka presented their experience gained during the multicenter study undertaken to seek the possibility of discontinuing infliximab therapy after acquiring low disease activity of RA and to evaluate progression of articular destruction during infliximab discontinuation. He showed that after reduction of disease activity of RA by infliximab treatment, approximately 55% of the 102 patients could discontinue infliximab for more than 1 year without radiologic progression of articular destruction.

The session was concluded with a presentation by Takayuki Sumida (University of Tsukuba, Japan) on 'Early Diagnosis and Treatment Evaluation of Rheumatoid Arthritis by Compact MRI' with focus on the use MRI as a useful tool for evaluating disease activity and therapeutic efficacy in rheumatoid arthritis. Their group developed a new 0.3 T low-field extremity MRI (compactScan, T-scan) and a compact MRI scoring system, with modified Outcome Measures in Rheumatology Clinical Trials – Rheumatoid Arthritis Magnetic Resonance Imaging Score (OMERACT-RAMRIS) scoring system. They suggested that conventional whole-body MRI was inconvenient on several levels. They compared the quality of T-scan, 0.3 T T-scan and 1.5 T whole-body MRI and concluded that T-scan is of the same worth as 1.5 T conventional MRI in the diagnosis of RA, although it is useful for the prediction of early-stage RA, and for evaluation of disease activity.

The afternoon plenary session 'Autoimmunity and Experimental Therapies' included talks on 'Hematopoietic Stem Cell Transplantation (HSCT) for Systemic Lupus Erythematosus: 10 years on' by Yvonne Loh (Singapore General Hospital, Singapore). He discussed that autologous HSCT could be a good approach for delivering high-dose immunosuppression in

an attempt to induce tolerance. In their experience, the hematopoietic stem cells were infused for two reasons: to shorten the period of neutropenia, and to permit regeneration of a more naive, and hopefully tolerant immune system in the absence of the original trigger for autoimmunity. In this session, Sita Naik (Lucknow, India) presented her experience on the role of potential anti-inflammatory agents from indigenous plants. The extracts of these plants have been shown to affect the expression of activator protein-1 and NFκB, which are critical transcription factors involved in the secretion of various inflammatory cytokines. These plants may have a modulatory effect on disease outcome and severity.

■ 13 September 2009

The last day of the congress began with a plenary session 'Autoimmunity at a Glance' chaired by Ashok Kumar (India) and Yaniv Sherer (Tel Aviv Sourasky Medical Center, Israel). The session started with a presentation on 'Vascular Rheumatology: Atherosclerosis and Angiogenesis in Autoimmune Diseases' by Z Szekanecz (Hungary) who discussed the role of vasculature in inflammation, angiogenesis and atherosclerosis associated with the pathogenesis of inflammatory rheumatic diseases. Lingyun Sun (Affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School, China) presented data on the clinical efficacy and safety of allogenic bone marrow-derived mesenchymal stem cells transplantation in patients with severe and treatment refractory SLE. An upregulation of Tregs was shown in all patients 1 week after mesenchymal stem cells transplantation. A drop in antinuclear antibody and anti-dsDNA titer was also reported. Zhe-Xiong Lian (University of Science and Technology of China, China) addressed the role of B cells in an experimental model of autoimmune cholangitis and reported that B cells had a suppressive effect on inflammatory response in the transgenic mice model of primary biliary cirrhosis. This was supported by an increase in disease severity of B-cell-depleted mice as well as amelioration of the disease caused by transferred pathogenic CD8⁺ T cell in the presence of PC-B cells.

The pre-lunch workshop was devoted exclusively to the available diagnostics in autoimmune diseases. The main highlight of the session was a lecture by Yehuda Shoenfeld on 'Predictive Value of Autoantibodies'. He described the role of autoantibodies in the prediction and prevention of autoimmune diseases through several examples of the utility of autoantibodies such as anticyclic citrullinated peptide in RA, anti-DNA, anti-RO in SLE. He also emphasized the use of vitamin D everyday by all individuals as it helps in the protection against several autoimmune diseases. K Conard (Germany) presented 'Automated HEP-2 Cell Assay for the Screening and Differentiation of Nonorgan Specific Autoantibodies'. He reported on the standardization of autoantibody testing by indirect immunofluorescence (IIF) on HEP-2 cells by automated interpretation systems. A novel fully automated IIF reading system with pattern recognition software has been developed (AKLIDES®, Medipan GmbH, Germany). Furthermore, to provide a standardized detection method of subcellular features, image acquisition, evaluation of image quality, image segmentation for object detection, feature extraction for object description, and classification of detected objects have been automatized. He concluded by saying that automated IIF reading allows a standardized identification of staining patterns of cellular and subcellular structures compared with the manual reading.

Future perspective

The 4th Asian Congress on Autoimmunity was a highly successful forum not only because it brought together physicians, immunologists and basic scientists from various parts of the world, but also provided a forum for developing possible

scientific collaboration between participants from various countries. In contrast to earlier conferences, this meeting was distinguished by including lectures on genetics and genomics and had separate sessions for discussing various diagnostic and therapeutic approaches related to immunological disorders worldwide.

The main highlights of the Congress were:

- SLE and rheumatoid arthritis were the most discussed disease models, along with newer diagnostic and therapeutic strategies used worldwide;
- Exposure to infectious agents may play an important role in the development of clinical manifestation of autoimmune diseases. On the contrary, infections have also been found to eradicate a variety of autoimmune diseases and, therefore, infection has been referred to as 'friends or foe';
- Vitamin D is an important immune modulator that plays an important role in the pathogenesis of autoimmune diseases and a minimum dose of 2000 IU/day has been found to be optimal for every individual;
- The immunogenetic aspects of autoimmune diseases reveals fundamental differences in disease associated HLA haplotypes at genomic level between Asian-Indian and Caucasian populations;
- The worldwide use of various strategies employing monoclonal antibodies targeting IL-6, IL17, IL-18 and other inflammatory cytokines were discussed in detail.

Among future meetings, the 7th International Congress on Autoimmunity will take place on 5–9 May 2010 in Ljubljana, Slovenia.