The First Israel-Italy Meeting on Advances in Autoimmunity and Rheumatology

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The First Israel-Italy Meeting on advances in Autoimmunity and Rheumatology was organized by Professors Elias Toubi, Dan Buskila and Yehuda Shoenfeld. The meeting took place at the Technion-Israel Institute of Technology’s Rappaport Faculty of Medicine in Haifa and was supported by the Italian embassy in Israel. Participants included clinicians from different fields, immunologists, rheumatologists and scientists. Talks were given by invited leading immunologists and rheumatologists from Italy and Israel and covered a wide spectrum of topics, among them the regulation of autoimmunity and the pathophysiology and management of rheumatic diseases. In this report I will highlight some of the interesting issues that were presented at the meeting.

NOVEL ASPECTS IN AUTOIMMUNITY

Prof. Shoenfeld opened the meeting with a review of the pathogenesis of autoimmune diseases. The pathogenic hypothesis comprises a complex interaction among genetic, environmental and hormonal factors that interact in an individual with a dysregulation of the immune system leading to disease development. A number of mechanisms could lead to the development of AIDs upon exposure to infections. These include molecular mimicry, bystander activation, polyclonal activation of B lymphocytes, epitope spreading, unveiling of cryptic antigens, and the exposure of super-antigens. Furthermore, several genes that are spread across the genome can contribute to the development of AIDs. In the complex mechanisms leading to the development of an AID, age and gender play a major role, mainly due to the influence of hormone levels. Sex hormones, in particular estrogen and prolactin, have an important role in modulating the immune response.

Nonetheless, major evidence suggests that before all these steps occur, what is necessary is a susceptible individual who develops autoantibodies over a long period. Such autoantibody production is genetically determined; and, finally, the presence of such antibodies seems to determine the clinical presentation of AIDs.

In the last ten years numerous new drugs have been used in the targeted therapy of autoimmune rheumatic diseases; the new drugs are mainly biotechnological products such as monoclonal antibodies and fusion proteins (biological). The immunogenicity of the biotechnological drugs was discussed by Prof. Guido Valesini (Italy). He stated that these proteins may induce the formation of anti-drug antibodies and this phenomenon may represent a dangerous side effect. Their immunogenicity may be influenced by several factors: firstly, the presence on the molecules of specific and restricted antigens such as allotypes and idiotypes. Immunoglobulin G allotypes are minor differences in the primary amino acid sequence between molecules of one IgG subclass that occur throughout a species. The idiotypes are on the Fab fragment, at or near the hypervariable regions of the heavy and light chains, and the actual antigenic determinant (idiotype) may include some of the framework residues near the hypervariable region. Anti-allotype antibodies may be induced by most of the monoclonal antibodies as well as by some fusion protein (often bound to Fc portion of human IgG1); anti-idiotypes are induced by human monoclonal antibodies. Other factors include the degree of humanization, the concomitant use of immunosuppressant drugs, the dosing regimen, the disease activity, and the route of administration. The formation of anti-drug antibodies may cause the neutralization of the drugs and the subsequent loss of efficacy of the treatment as well as some hypersensitivity reactions. Several studies have demonstrated the production of anti-drug antibodies in patients suffering from rheumatoid arthritis, spondyloarthritis, inflammatory...
bowel diseases and psoriasis under treatment with an anticytokine product such as anti-tumor necrosis factor-alpha [1]. Prof. Roberto Perricone (Italy) reviewed the role of the complement system in autoimmune diseases. The complement system is a component of the innate immune system. In recent years, the immunoregulatory functions of the complement system were demonstrated and it was determined that the complement proteins play an important role in modulating adaptive immunity and in bridging innate and adaptive responses. When the delicate mechanisms that regulate this sophisticated enzymatic system do not function correctly, the complement system may cause damage, mediating tissue inflammation. The complement system is involved in the pathogenesis and clinical manifestations of several autoimmune diseases, such as systemic lupus erythematosus, vasculitides, Sjögren’s syndrome, antiphospholipid antibody syndrome, systemic sclerosis, dermatomyositis and RA [2]. On the other hand, complement deficiency has been associated with increased risk for autoimmune disorders. Because of its functions, the complement system is an attractive therapeutic target for a wide range of diseases. To date, several compounds interfering with the complement cascade have been studied in experimental models for autoimmune diseases. The main therapeutic strategies are inhibition of complement activation components, inhibition of complement receptors and inhibition of membrane attack complex. However, none of the available agents was proven to be both safe and effective for treatment of autoimmune diseases in humans. Dr. Nancy Agmon-Levin (Israel) highlighted the link between a low level of vitamin D and autoimmune and immune mediated diseases such as SLE, RA and multiple sclerosis. In recent years, vitamin D has been linked with various metabolic and immunological processes and its role has emerged from a hormone related only to bone metabolism to an essential component of human health preservation. Vitamin D has been accepted as a natural immune modulator of various metabolic and immunological processes and its role has emerged from a hormone related only to bone metabolism to an essential component of human health preservation. Vitamin D is emerging from a hormone related only to bone metabolism to an essential component of human health preservation.

Epidemiological data underline a strong correlation between poor vitamin D status and higher risk for chronic inflammatory illnesses of various etiologies, including autoimmune diseases. Different epidemiological, genetic and basic studies have indicated a potential role of vitamin D in the pathogenesis of certain systemic and organ-specific autoimmune diseases. Many of these studies demonstrated a correlation between low vitamin D and disease appearance and/or manifestations. In addition, vitamin D receptor polymorphisms observed in some of these autoimmune diseases may further support a plausible pathogenic link [3]. Notably, some autoimmune diseases were not related to vitamin D status when compared to healthy subjects. In this context the question of vitamin D supplementation in patients suffering from autoimmune diseases should be addressed. Thus, although further studies are needed, the supplementation of vitamin D in disease of up to 4000 IU/day should be considered.

**APLS PREGNANCY AND CYTOKINES**

The importance of antiphospholipid antibodies in pregnancy was discussed by Prof. Pier Luigi Meroni from Italy. In vitro studies have documented that beta2 glycoprotein I binds to endothelial cells and trophoblasts. This finding might explain how circulating aPL can affect the functions of these cells, contributing to the thrombophilic diathesis and to the aPL-associated fetal losses [4]. Owing to the potential technical artifacts of in vitro cell cultures and the lack of any direct demonstration of β2GPI on tissues in vivo, Prof. Meroni and his associates recently set up an innovative experimental model to investigate this aspect for the first time. They analyzed the in vivo distribution of cyanine 5.5-labeled β2GPI in mice and evaluated the effect of pregnancy and circulating antibodies on its tissue localization. In addition, they also investigate whether pro-inflammatory stimuli (i.e., lipopolysaccharide) may affect β2GPI tissue expression. The signal from the labeled molecule was evaluated by whole-body scan and by atomic force microscopy on tissue sections from the treated animals. The intravenous infused Cy5-5 β2GPI was detected in the liver by whole-body scan and then excreted in the urine of naive mice. No binding at all to the vascular endothelium was found with the only exception of the staining of uterine EC. Pregnancy modified the tissue distribution by enhancing its localization on EC and trophoblasts at the embryo implantation sites. Placentas and umbilical cords gave the strongest signal in agreement with the previous demonstration of placental distribution of β2GPI and its expression on human EC from umbilical cord veins. Mice immunized with human β2GPI and producing antibodies reacting with human but not the murine molecule showed a similar β2GPI biodistribution to naive mice, but the immunized pregnant animals exhibited a significant increase in fetal loss associated with C3 and C9 deposition at the implantation sites. Treatment of mice with lipopolysaccharide after β2GPI-Cy5.5 injection promoted protein localization on gut and brain EC associated with IgG, C1q, and C9 deposition in immunized mice. These findings indicate that β2GPI binding to EC requires priming with pro-inflammatory factors which is not needed for uterine and placental localization.

**Abbreviations**

RA = rheumatoid arthritis
SLE = systemic lupus erythematosus
β2GPI = beta2 glycoprotein I
Cy5.5 = cyanine 5.5
EC = endothelial cells

**Notes**

[1] APLS = antiphospholipid antibody syndrome
aPL = antiphospholipid antibodies
β2GPI = beta2 glycoprotein I
Cy5.5 = cyanine 5.5
EC = endothelial cells
Prof. Angela Tincani (Italy) discussed the possible risks and complications of treating systemic rheumatic diseases in pregnant women. Probably the first challenge is to preserve fertility when using gonadotoxic drugs by inducing a temporary menopausal state by gonadotropin-releasing hormone analogues. Pregnancy planning should be discussed by physicians with their patients, even when it does not seem to be in the near future. In fact, before conception, teratogenic drugs must be substituted, but the efficacy of the new treatments must be verified before gestation. Different rheumatic diseases have different effects on pregnancy outcome: SLE, especially when linked to APLS, carries the higher rate of pregnancy losses and complications that can in part be prevented by careful multidisciplinary management. On the other hand, pregnancy can worsen maternal disease, particularly if the disease is still active at conception or has already caused internal organ failure. Finally, the observation of an increased rate of learning disabilities in children of mothers with systemic rheumatic diseases suggests careful monitoring to identify the subjects who should be helped to overcome their difficulties.

Prof. Caterina De Carolis (Italy) added information to this important issue. In normal pregnancy, the maternal immunological response against trophoblast antigens, concomitant with a transient depression of maternal cell-mediated immunity to protect the semiallogenic embryo from rejection, is the predominant mechanism causing high live birth rate. Successful pregnancy is considered a Th1-Th2 cooperation phenomenon, with a predominantly Th2-type lymphocyte response. Failure in the generation of Th2-type responses is associated with recurrent spontaneous abortion, obstetric complications and poor pregnancy outcome. A deeper insight into apparently unexplained infertility and recurrent spontaneous abortion shows increasing evidence supporting both alloimmune and autoimmune mechanisms, in which natural killer cells and autoantibodies seem to play a relevant role. SLE is the autoimmune disease that most commonly jeopardizes pregnancy, with potential adverse events including miscarriage, intrauterine fetal restriction, congenital heart block, preterm delivery, and flares of lupus activity. The most important predictors of poor obstetric outcome are lupus activity and the presence of aPL that together may result in the APLS. Anti-thyroid antibodies and aPL in SLE are associated with reduced fertility, miscarriage and preterm delivery, but the precise mechanisms by which thyroid antibodies, as well as those against other tissues, are suppressed during pregnancy and often exacerbate after delivery, remain obscure. Presumably, the rapid reduction in immune suppressor functions following delivery leads to the reestablishment and/or exacerbation of these conditions. Also uterine NK cells comprise the largest population at the implantation site, and their activity, characteristics and abundance suggest that they participate in the “decidualization” process, that, vice versa induces NK activation and recruitment in each menstrual cycle. However, NK cell alteration may be associated with impaired pregnancy, and the modulation in the number of circulating NK cells is most likely to be a primary event rather than an active inflammation/drug administration consequence during an inflammatory/autoimmune process, thus playing an important role in the pathogenesis of immunological infertility [5].

Prof. Miri Blank (Israel) discussed the possible connection between tetanus toxoid vaccine and APLS. Licensed vaccines are mostly safe, but in rare cases may be associated with humoral response to self antigens due to molecular mimicry, epitope spread, bystander activation, or polyclonal triggering. Moreover, a clinical picture of autoimmune conditions following post-vaccination is rare. Nevertheless, anecdotal case reports on flare of autoimmune response with clinical manifestations have been reported. The clinical pictures occur in the framework of ASIA – Autoimmune Syndromes Induced by Adjuvants, coined Shoenfeld’s syndrome [6]. A synthetic peptide with therapeutic potential was identified by introducing antiphospholipid (anti-β2GP1) monoclonal antibody derived from an individual vaccinated with TT to a peptide phage display library. Using bioinformatics, this peptide had high homology (one mismatch) with several bacteria and viruses including TT. In order to prove molecular mimicry, Prof. Blank et al. purified the anti-TT/peptide Abs from mice immunized with TT. These Abs were able to induce experimental APLS in naïve mice. Moreover, healthy individuals vaccinated with TT have differential elevated titers of anti-TT/peptide Abs. Prof. Miri Blank concluded that TT is a very important vaccine in recent decades. In rare cases, with a specific genetic background, it may lead to the ASIA picture.

**ADVANCES IN SLE AND RA**

Pointing to new avenues in the study of the pathogenesis of SLE, Dr. Zehava Vadasz (Israel) reported on the association between semaphorin 3A and SLE disease activity. Sema3A was initially found in neurodevelopment and in recent years was found to be important in angiogenesis and the immune system. In her recent study she found serum sem3A to be inversely correlated with SLE disease activity. Moreover, it was shown that serum level of sema3A < 50 ng/ml may predict kidney involvement and anticardiolipin antibodies in SLE patients. She also demonstrated that sema3A has regulatory properties, inducing altered Toll-like receptor-9 expression on ODN-stimulated B cells from SLE patients. Also, other regulatory molecules on B cells were found to be up-regulated by sema3A, namely, CD72, transforming growth factor-beta.

**NK = natural killer**

**TT = tetanus toxoid**

**sema3A = semaphorin 3A**
and neutrophilin-1. This suggests that sema3A may become an immunomodulatory agent in treating SLE [7].

Prof. Andrea Doria from Italy reviewed the clinical therapeutic use of belimumab in SLE patients. Belimumab is a fully human monoclonal antibody that selectively targets and inhibits soluble B lymphocyte stimulator, also called B activating factor. Inhibition of BlyS can result in autoreactive B cell apoptosis. BlyS promotes B cell survival, differentiation, proliferation, immunoglobulin secretion and class switching. The most important biologic effect of BlyS on B cells is to drive B2 cell survival, particularly after the transitional stage 1 (T1), thus promoting the survival of transitional stage 2 (T2) B cells, marginal zone B cells that mediate T cell-independent response, and follicular B cells that mediate T cell-dependent response.

The relevance of BlyS to human SLE is supported by a number of observations: SLE patients have elevated levels of BlyS in their serum as well as in cerebrospinal fluid, high serum levels of BlyS are correlated with anti-dsDNA antibody levels and with disease activity score, and SLE patients have increased expression of mRNA for BAFF receptor and TACI in peripheral blood mononuclear cells. In a phase II randomized controlled trial that did not meet the primary endpoint, it was shown that belimumab depletes B cells but not T cells (CD20 were reduced by about 60–70%); it immediately depletes naïve and transitional B cells, decreases CD27+IgD+ memory B cells and plasma cells after 1 year. By contrast, BAFF blockade has little or no effect on class-switched memory B cells. Notably, this phase II randomized controlled trial showed a significant decrease of SELENA-SLEDAI score in a subgroup of serologically active patients. These results led to the establishment of two large phase III randomized control trials, named BLISS-52 and BLISS-76. The designs of the two studies were exactly the same except for the duration of the study – 52 weeks and 76 weeks respectively. Patients with mild-to-moderate disease activity who were stable in their baseline treatment for at least 6 months were randomized to receive placebo, belimumab 1 mg/kg or belimumab 10 mg/kg plus the standard of care. Both studies met their primary endpoints, showing a higher frequency of clinical response in patients treated with belimumab in addition to standard of care compared with those treated with standard of care alone. The results were confirmed in the pool analysis. Belimumab plus standard of care was generally well tolerated, with a safety profile comparable to that of placebo plus standard of care. Following these significant positive results in both phase III studies, belimumab obtained the registration for lupus by the Food and Drugs Administration and is presently under evaluation by the European Medicines Agency. However, the magnitude of the results of the two BLISS studies at 52 weeks and the lack of effect of belimumab at 76 weeks in BLISS 76 have been questioned. In this regard, it must be mentioned that prednisone tapering during belimumab treatment may restore residual disease activity. Hence, a delicate balance is orchestrated between lowered steroid dosage and dampening of disease activity. Notably, patients enrolled in these studies, who represent the ideal target for belimumab, had low but chronic disease activity while they were receiving a stable standard of care treatment: prednisone plus hydroxychloroquine and/or immunosuppressants. In other words, these are patients with a chronic active disease despite the standard treatment. It is clear that in this condition it is very difficult to demonstrate the additive effect of a drug [8,9].

Using autoantibodies in the diagnosis of SLE is important. Prof. Nicola Bizzaro (Italy) discussed the use of anti-chromatin versus anti-dsDNA antibodies in the diagnosis of SLE. Prof. Bizzaro conducted a systematic review and a meta-analysis of all the studies published in the last 15 years on the diagnostic accuracy of the analytical methods to search for ANuA. He selected 26 articles providing data on both ANuA and anti-dsDNA antibody assays in the same series of patients. The systematic review and meta-analysis showed that the overall sensitivity of the ANuA assay is 61% (confidence interval 60–62) and the specificity 94% (CI 94–95). The overall positive likelihood ratio is 13.81 (CI 9.05–21.09) and the negative likelihood ratio 0.38 (CI 0.33–0.44). The odds ratio for having SLE in ANuA-positive patients is 40.7. The comparative analysis on anti-dsDNA antibodies conducted on the 26 studies which provided data for both antibodies showed that ANuA have greater diagnostic sensitivity (59.9% vs. 52.4%) and a specificity rating only slightly higher (94.9% vs. 94.2%). The probability that a subject with positive ANuA has SLE is 41 times greater than a subject with negative ANuA, while for anti-dsDNA the probability is 28 times greater. These numbers are even more impressive in children, in whom ANuA have an odds ratio for the diagnosis of SLE of 146, compared to 51 for anti-dsDNA antibodies. In selected studies, ANuA (P < 0.0001) but not anti-dsDNA antibodies (P = 0.256) were significantly associated with disease activity measured by the international score systems. However, neither antibody appears to correlate with kidney involvement. In conclusion, ANuA have equal specificity but higher sensitivity and prognostic value than anti-dsDNA antibodies in the diagnosis of SLE. Despite a certain heterogeneity among the various studies, the use of ANuA appears more efficacious than anti-dsDNA [10].

### Clinical Aspects in Autoimmunity and Rheumatology

According to Prof. Dan Buskila (Israel), recent studies suggest that genetic factors can play a significant role in the perception

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**BlyS =** B lymphocyte stimulator  
**BAFF =** B activating factor  
**CI =** confidence interval
of pain and the development of a co-morbid pain condition. A strong familial aggregation is reported in fibromyalgia syndrome and related conditions (central sensitivity syndromes). Polymorphisms of genes in the serotoninergic, dopaminergic and catecholaminergic systems have been reported in these chronic pain states and may play a role in its pathogenesis. The mode of inheritance of FMS is unknown, but it is most probably polygenic. Environmental factors including trauma and stress may trigger the development of FMS in genetically predisposed individuals. Recognition of these gene polymorphisms may help to better subgroup FMS patients and to treat them with a more targeted pharmacological approach [11].

Prof. Carlo Selmi (Italy) discussed the sex differences in autoimmunity. The majority of autoimmune diseases recognize a striking female predominance, in most cases exceeding 9 to 1. The role of sex hormones and reproductive factors has been supported by numerous lines of evidence but definitive conclusions are lacking; these factors were comprehensively discussed elsewhere in this seminar. This presentation included some unsuspected factors related to the sex imbalance observed in autoimmunity. First, studies on X chromosome changes revealed that women with systemic and tissue-specific autoimmune diseases (with the exclusion of SLE) manifest a higher rate of X monosomy in peripheral lymphocytes. Similarly, the epigenomics of the X chromosome in monozygotic twins discordant for the autoimmune phenotype identified numerous X chromosome genes differentially methylated in this unique set of patients and controls. Second, numerous risk factors for autoimmune diseases are more pertinent to women and may partially explain the observed imbalance or impact of the X chromosome in epigenetics. Third, we cannot rule out that different degrees of physician awareness may underestimate the disease incidence in men, as the female predominance is significantly lower when autoantibody positivity rates are compared between sexes. Fourth, we should also consider that economic differences are commonly associated with the risk of autoimmune disease and should be accounted for in association studies [12].

Dr. Gisele Zandman-Goddard (Israel) summarized the updated knowledge regarding the environmental triggers in SLE that are encountered in a variety of disease entities. While each entity has been recognized as a specific disease with its own diverse clinical and serological pattern, one could argue that many findings are common. Could it be that environmental factors associated with SLE also play a role in the different entities of this spectrum? Cutaneous lupus was associated with exposure to ultraviolet light, drugs, and smoking. A rare form, lupus erythematosus tumidus, developed after sex reassignment surgery and suggests that the artificial female hormone milieu may induce lupus in a non-predisposed male individual. In contrast to classic drug-induced lupus erythematosus, when induced by anti-TNF blocker it induces classic SLE, often severe, with elevated titers of anti-dsDNA antibodies and requires immunosuppressive therapy. In SLE, exposure to exogenous estrogens, not only oral contraceptives or hormone replacement therapy, but industrial sources such as pesticides, phytoestrogens found in soya and tofu, and phthalates found in plastic bottles are sources of estrogen. Cosmetics such as skin-whitening cream, nail polish and lipstick contain metals that may cause damage. Exposure to solvents through recreation or occupation is linked to undifferentiated connective tissue disease.

Prof. Ferdinando Nicoletti (Italy) reported on the novel therapeutic approaches to abrogate the biological activities of macrophage migration inhibitory factor [13]. MIF is a pro-inflammatory cytokine characterized as a soluble product of activated T lymphocytes that inhibits macrophage migration in vitro. MIF is expressed by a variety of cell types including epithelial, endothelial and immune cells. It binds to a cell surface receptor CD74 or to an intracellular receptor JAB1. MIF acts through enhancement of TLR4 expression, phagocytosis, intracellular killing, nitric oxide, H₂O₂ and TNFα production in macrophages, thus representing an important factor in protection of the host against various infectious agents. Through induction of interleukin-12 and inhibition of IL-10 synthesis, MIF favors Th1 immune response. Therefore, MIF could represent a major cytokine in the pathogenesis of autoimmune diseases. During both systemic and organ-specific autoimmune disease over-production of MIF can augment inflammation and favor the priming of ignorant autoreactive T cells.

The role of MIF has been studied in several models of type 1 diabetes. In both spontaneous and accelerated animal models of T1D in non-obese diabetic mice, high MIF expression was found in splenic lymphocytes. This elevated MIF production is thought to support the recruitment of immune cells to the islets causing insulitis and diabetes. Also, the immunoneutralization of MIF with monoclonal antibodies prevents streptozotocin and cyclophosphamide-induced diabetes in NOD mice. MIF seems crucially involved in Guillain-Barré syndrome and experimental allergic neuritis, the animal counterpart of the human disease. Increased MIF plasma levels have been found in GBS patients as compared to healthy controls, and progressive increase of MIF circulating concentration correlates with the patient’s disability. To evaluate the role of MIF in the development of EAN, Prof. Ferdinando Nicoletti tested the effect of two specific inhibitors of MIF, a neutralizing monoclonal

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antibody or a chemical inhibitor ISO1 on the course of murine EAN. Both anti-MIF mAb and ISO1 favorably influenced the course of EAN.

MIF has also been implicated in the pathogenesis of SLE. Elevated serum MIF levels have been found in SLE patients and correlated with lupus-related disease damage. Moreover, MIF is highly expressed in renal tissue, and the skin lesions in lupus-prone MRL/lpr mice and MIF deficiency attenuate macrophage recruitment, glomerulonephritis and lethality of these mice.

Dr. Alexandra Balbir-Gurman (Israel) presented her department’s experience in systemic sclerosis. They analyzed clinical and laboratory data on 219 SSc patients, who were divided into three subgroups according to autoantibody status: antitopoisomerase (Scl-70+, 37%), anticentromere (ACA+, 34%), and antinuclear (ANA+, Scl-70-/ACA-, 29%) antibodies. Analysis of the clinical data revealed that ACA+ patients were older, had only limited skin disease with longer disease duration, and did not develop significant interstitial lung disease or scleroderma renal crisis, but had high mortality from PAH. Scl-70+ patients often had diffuse skin disease and highest Rodnan skin scores; severe ILD and secondary PAH, heart involvement but also SRC were main organ-specific complications. ANA+ patients more often had overlap syndrome, mainly SSC and myositis, diffuse skin disease and multiple digital ulcers; ILD, gastric involvement with gastric antrum vascular ectasia and SRC were main organ-specific complications. Mortality was higher in the Scl-70+ and ACA+ group compared to ANA+ and to the whole group. They concluded that presence of Scl-70+ or ANA+ will dictate monitoring on kidney function and blood pressure as well as restriction in the use of high steroid doses to prevent the development of SRC [14]. Professor Brik (Israel) reviewed the tremendous change in the prognosis and quality of life of children with rheumatic diseases following the new era of biologic treatment.

To conclude, this meeting marks an important milestone in the scientific relationship between Israel and Italy and I hope that it will be the beginning of a fruitful tradition that will be continued.

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