Controversies in Systemic Lupus Erythematosus and Antiphospholipid Syndrome

HIGHLIGHTS

Fondazione
Internazionale
Menarini

Florence (Italy)
April 28th – 30th, 2016

HIGHLIGHTS

Welcome to Florence!

Prof. Prisco and Prof. Emmi, Chairmen of the Convention, opened the congress works by stressing the importance of clinical research as a concrete instrument for improving healthcare. Prof. Dei, Rector of the University of Florence, greeted researchers from all over the world who are all linked by a common denominator: their passion for research combined with a high scientific profile. Prof. Cantone, president of the Italian Association "Italian Group for the fight against Systemic Lupus Erythematosus Onlus", gave a brief presentation of the activities of the association which has as its main objective that of helping patients suffering from Lupus to live "without Lupus", that is, as far as possible free from the effects of this disease. Prof. Emmi, co-Chairman of the convention, underscored the interdisciplinary aspects of the two diseases, subject of the congress, the treatment of which calls for the involvement of professionals from the majority of different medical disciplines, well beyond those normally involved, such as rheumatology and internal medicine.

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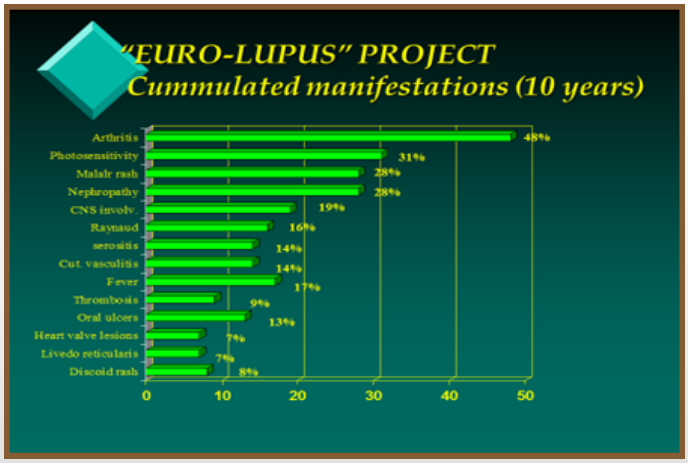
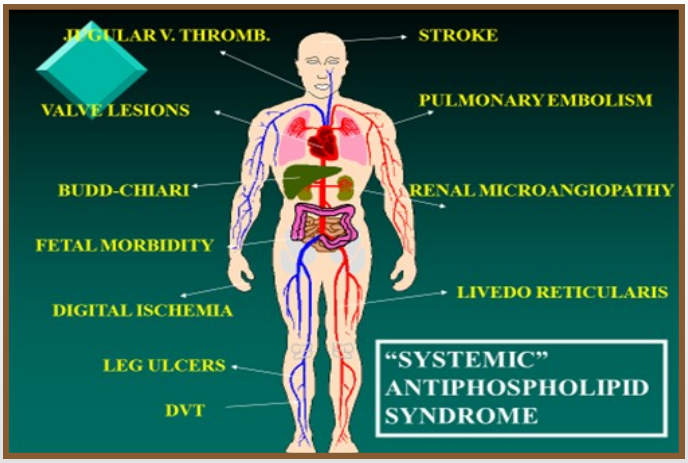
Systemic Lupus Erythematosus and the Antiphospholipid Syndrome: at what stage are we?

Ricard Cervera
(Barcelona, Spain)

In his speech, Prof. Cervera from Barcelona presented the two European projects on Systemic Lupus Erythematosus (SLE) and the Antiphospholipid Syndrome (APS) starting from their conception in 1990 up until today. The two projects are similar; both have as their goal the study of the morbility and mortality of 1,000 young patients suffering from SLE and APS respectively. As far as SLE is concerned, patients at a young age are affected by more severe forms of the disease compared to adult patients. In particular, SLE affects more women than men and there are profound differences in the symptoms depending on the age of onset, the gender of the patient and the specific auto-antibodies present. The 10-year results of the SLE project have shown a satisfactory survival rate equal to 93%. Another interesting aspect is represented by the fact that the inflammatory phase is prevalent during the first years after onset of the disease. The thrombotic complications are the main cause of the long-term morbility and mortality. As far as APS is concerned, this is a syndrome that affects young-adult patients more frequently, and usually of the female sex. In half of the cases, the manifestation of the syndrome is primary, while in 40% of cases its onset takes place on a pre-existing condition of SLE. It is characterised by thrombotic phenomena with a systemic onset in the body. The pharmacological treatment is based on the administration of anticoagulant and antiaggregant drugs and the main complication is bleeding that can occur indifferently in any of the various organs. This is a disease characterised by a high mortality rate that manifests at an average age of 59 years. The main cause of death is due to the onset of bacterial over-infections apparently not correlated to the progress of the disease.





What are the main characteristics of the two study projects? What is the most frequent age of the onset of SLE? What are the main differences observed in the forms of paediatric SLE compared to those present at an adult age? What are the main neurological symptoms of APS?

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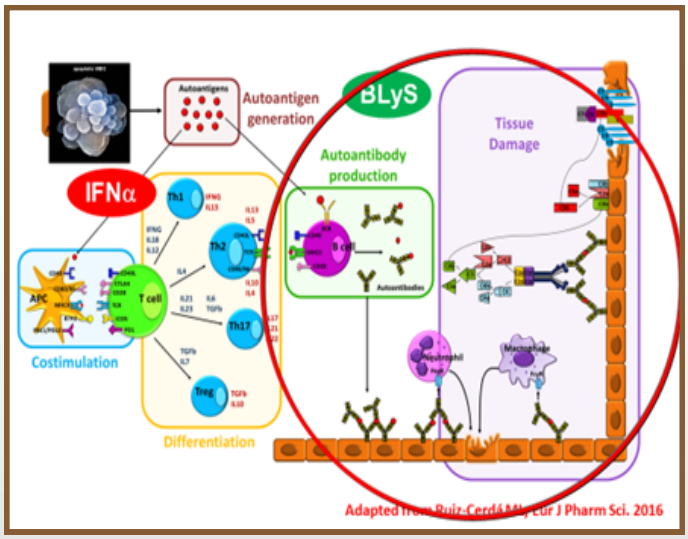
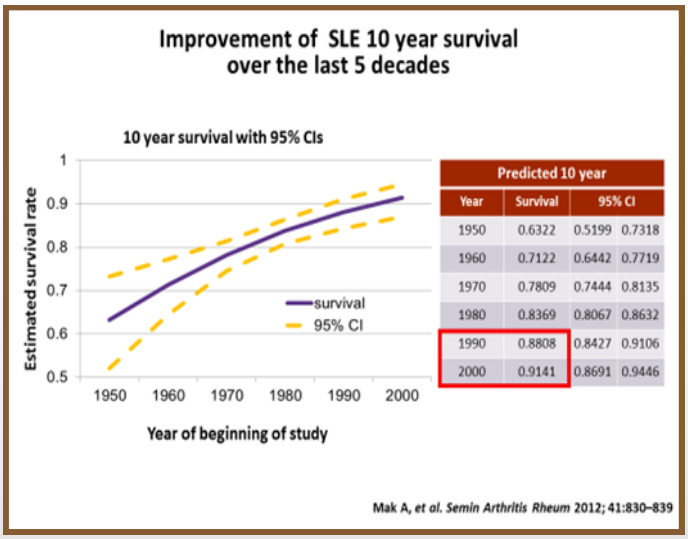
The pathogenesis of SLE

Zahir Amoura
(Paris, France)

Prof. Amoura from Paris spoke about the pathogenesis of SLE starting from immunisation against "apoptotic bodies" released in the circulation during the course of the disease. These molecules are the triggering factor for the genesis of autoimmune phenomena characterised by the production of auto-antibodies that react against specific nuclear factors. The generated immune complexes are deposited in the tissues and via the complement activation, produce local alterations and damages. During these processes, various cytokines are involved and in particular, interferon α, which is the principal driver of inflammation in patients suffering from SLE. The speaker then described the pharmacological studies currently in progress with new molecules: anti-interferon α, ɤ monoclonal antibodies and cytokine inhibitors. The data produced are encouraging: in the case of anti-interferon α monoclonal antibodies, more than 30% of patients suffering from SLE achieved the study objectives. The speaker concluded his talk by stating that thanks to the improvements in the knowledge of the physiopathology of SLE and the drugs developed over recent years, the medium-long term prognosis has improved significantly and has reached a survival rate at 10 years equal to 90%.





What are the main physiopathological mechanisms that give rise to the onset of SLE? What is the effect of the principal monoclonal antibodies developed to treat SLE? Is there still room for the historic pharmaceutical products used for the treatment of SLE?

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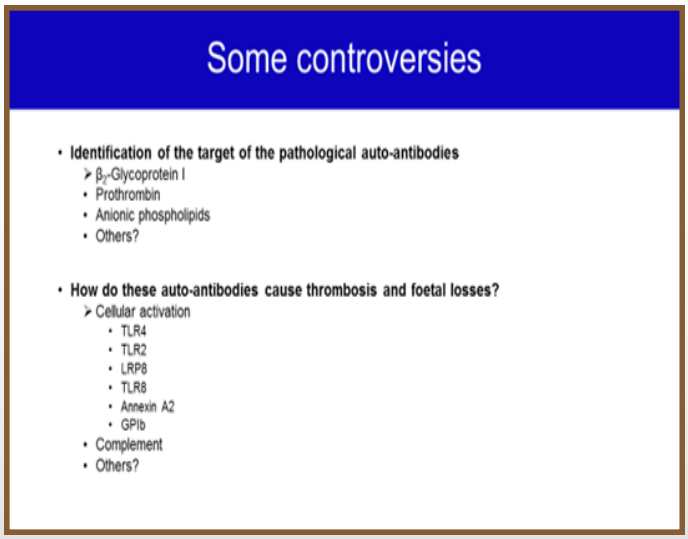
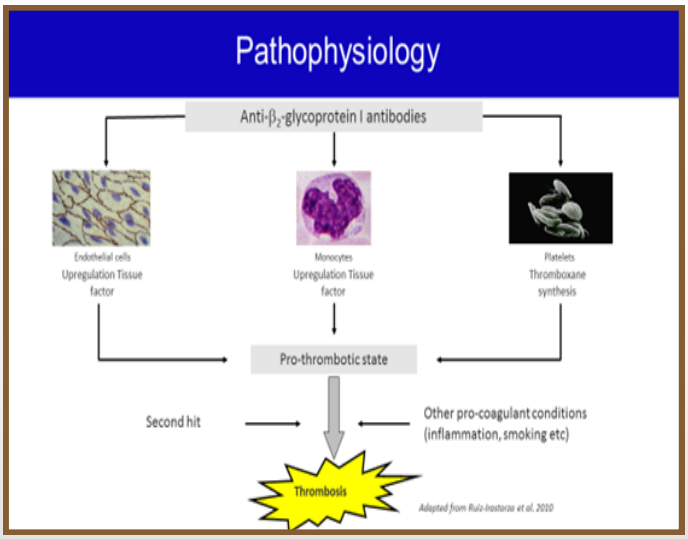
The pathogenesis of APS: new acquisitions

Philip G. de Groot
(Utrecht, Nederlands)

Prof. de Groot from Utrecht addressed the issue of the pathogenesis of APS and stressed how there are different theories, all based on the possible mechanisms responsible for the activation of the thrombotic pathway typical of this syndrome. The molecules taken into examination as possible targets of the activity of the auto-antibodies are β_2 glycoprotein I, prothrombin and the anionic phospholipids. Nevertheless, it is not sufficient to identify the target molecules since it is also necessary to identify the mechanism that gives rise to the interaction between the auto-antibodies and the target molecules. The speaker presented a series of data taken from studies mainly conducted on animal models for the purpose of presenting a specific physiopathogenetic theory based on the uptake of the antiphospholipid antibodies by the circulating cells such as monocytes, enthothelial cells and platelets. The next step is represented by the endocytosis of these auto-antibodies which are in turn responsible for the so-called cellular activation that manifests with the activation of the "tissue factor" and the complement activation. The speaker stressed how the cellular activation may be possible thanks to the action of different receptors located not only at the level of the cell membrane but also at the level of the exosomes that determine dual "internalization" of the auto-antibodies: the first at a cytoplasmatic level and the latter at a nuclear level. The complement activation is in turn responsible for the systemic thrombotic pictures typical of this syndrome.





What is the principal pathogenetic pathway responsible for the thrombotic manifestations typical of APS? How does the endocytosis of the auto-antibodies take place? What are the main theories formulated for explaining the cellular activation? What is the effect of the inhibition of the complement in patients suffering from ASP?

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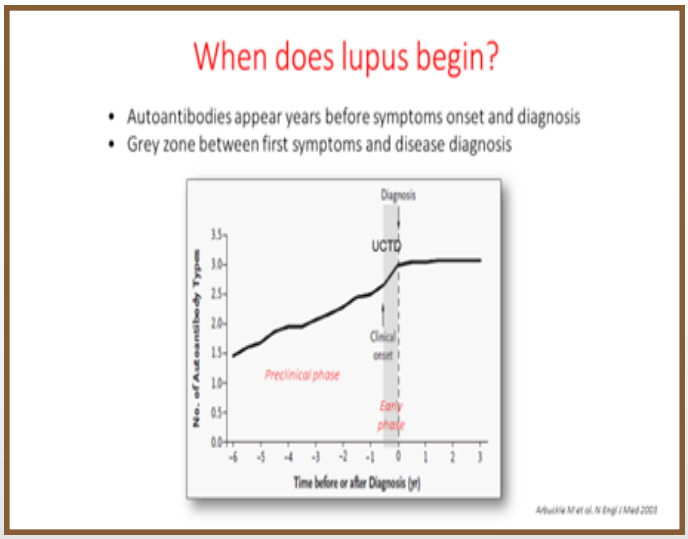
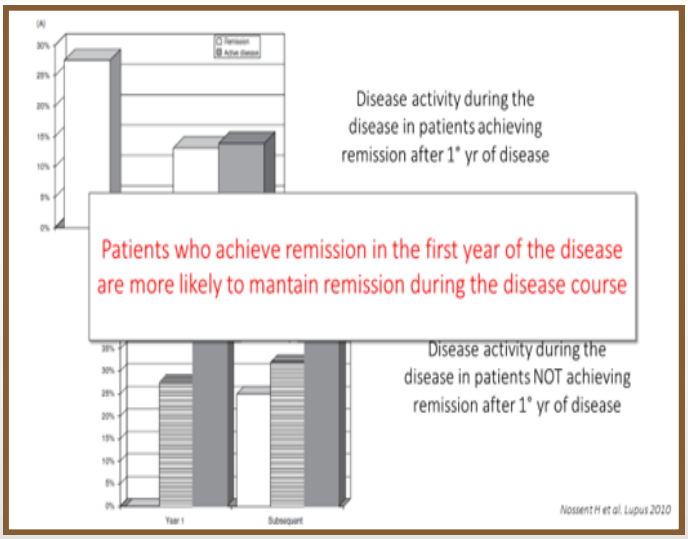
Systemic Lupus Erythematosus: Symptomatology and diagnosis

Marta Mosca
(Pisa, Italy)

Prof. Mosca from Pisa addressed the topic of the diagnosis of the disease and its activity status. The primary key point is the fact that there is the onset of symptomatology and some metabolic indicators years prior to the classical clinical manifestation that makes it possible to diagnose SLE. In addition, not all patients who have early signs and symptoms of SLE will develop a full-blown picture of the disease. These data place the physician in a difficult position when faced with the situation of having to establish the diagnostic instruments and the early pharmacological treatment. Another aspect pointed out by the speaker is the absence of diagnostic biomarkers during the early stages of disease. As far as the so-called "activity status" is concerned, the speaker affirmed that patients who manage to achieve remission during the first year of the disease are more likely to maintain remission throughout the entire course of the disease itself. The activity of the disease is associated with organ damage and correlated to the increased risk of mortality. The quality of life is also worse in patients suffering from SLE in the active status. She spoke about the indexes of the disease and the parameters that can be used to diagnose the state of remission. There is a new project underway that has as its objective the redefining of the remission-indicating parameters which, starting from the typical clinical signs and symptoms, also involve the real lives of the patients.





When does SLE start? How much do the classification criteria help in the early diagnosis of SLE? Is SLE a single disease, or a syndrome characterised by a series of symptomatological manifestations? What is the impact of the activity of disease on the future evolution of the patients?

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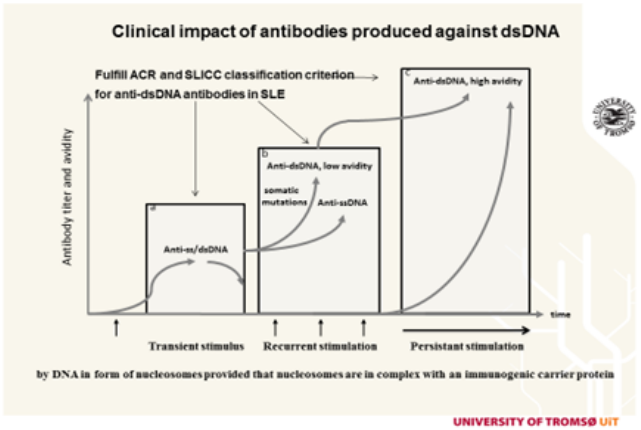
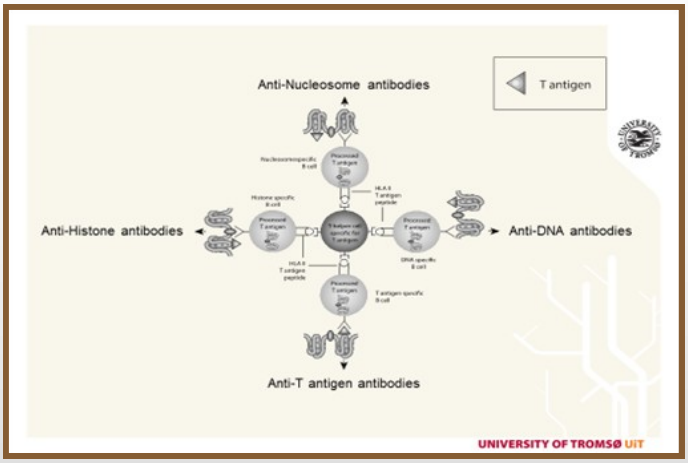
The anti-DNA antibodies: dogma and controversies

Ole Petter Rekvig
(Tromsø, Norway)

Prof. Rekvig from Tromsø addressed the topic of the anti-dsDNA antibodies present in patients suffering from SLE and other diseases such as infective and neoplastic conditions. After six decades of study no unanimous consent has yet been reached regarding their origin and their impact in pathogenetic terms. In fact, the anti-DNA antibodies are not specific for the double helix structure of DNA. They may be associated with innumerable other fractions of DNA but above all, they are not specific for SLE, in the sense that there may be patients suffering from SLE without any anti-dsDNA antibodies and vice-versa, patients in whom these auto-antibodies are present but who are not suffering from SLE. The speaker presented a model developed by a study group that explains the genesis of these auto-antibodies generated, starting from the specific T-helper cells for T antigens: in the presence of specific B cells for the nucleosomes, these T antigens are able to bond the T-helper cells and create the specific auto-antibodies for the nucleosomes and for DNA. In order for this bonding to occur, the presence of a viral infection, even banal, is essential during which a viral protein capable of bonding the DNA of another organism, bonds with the autologous nucleosomes, thus triggering the autoimmune process. These auto-antibodies, present in infective states, may also still be present in patients suffering from SLE as has been demonstrated in an experimental manner via the induction of anti-DNA antibodies and anti-nucleosomes, starting from the autologous nucleosomes. Subjects with immune profiles considered normal can also develop anti-DNA antibodies in the same way in the presence of parasitic, bacterial or viral infections, as well as in various neoplastic forms. The speaker therefore concluded by pointing out that the anti-dsDNA antibodies are not specific biomarkers for SLE per se, nevertheless, when they are present in patients suffering from SLE, they express their pathogenetic potential thanks to their ability to mark exposed fraction of extracellular chromatin.





What is the origin of the anti-dsDNA antibodies? What is the role of viral infections in the development of these auto-antibodies? How are these auto-antibodies produced in patients suffering from SLE? How can the Lupus Nephritis model help in determining the genesis of the anti-dsDNA antibodies in patients suffering from SLE?

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Management of pregnancy in patients suffering from SLE

Michelle Petri
(Baltimore, USA)

Prof. Petri from Baltimore presented data on an extremely important topic in view of the risk to which patients suffering from SLE are exposed in case of a pregnancy. In fact, an exacerbation of the disease is frequently observed in pregnant women and as a result, it is necessary to increase the dosage of prednisone, which is obviously not healthy for the foetus. In these conditions, the incidence of preterm births increases, as well as premature rupturing of the membrane and the onset of signs and symptoms of pre-eclampsia. All these conditions significantly increase the incidence of spontaneous abortions. As far as the mothers are concerned, they are at the risk of mortality, the rate of which is at least 20-fold higher compared to women not suffering from SLE. The exacerbation of the disease during pregnancy is often accompanied by a deterioration of the kidneys, while skin and joint lesions tend to improve. In these conditions, spontaneous abortions increase exponentially and there is a reduction in the number of term births while the foeti tend to be smaller than their gestational age. The speaker then went on to address the topic of the anti-SLE therapy to be implemented during pregnancy, by presenting data on the use of prednisone and hydrochlorochine, and on the main adverse events deriving from the use of prednisone. She lastly addressed the topic of pregnancy during APS and presented data on the complement activation in these patients and on the use of heparin and aspirin in relation to their effect on the foetus.

Pregnancy in SLE

- SLE pregnancies are high-risk
- Lupus flare, requiring increased doses of prednisone, is common
- Preterm birth, pre-eclampsia and premature rupture of membranes are increased
- Pregnancy loss is increased in women with active lupus or antiphospholipid antibodies

Adverse Events Associated with Prednisone Therapy

	Frequency of Complication		
Highest Dose (mg)	Diabetes	Hyper-tension	Pre-eclampsia
0-9	5	25	20
≥ 10	15	53	38
P-value	NS	0.0007	0.05

How useful is dosing the complement for predicting the risks for the mother and foetus during pregnancy? How much does the prognosis worsen in pregnant patients suffering from SLE? What are the most commonly used pharmaceutical products in pregnant women suffering from SLE?

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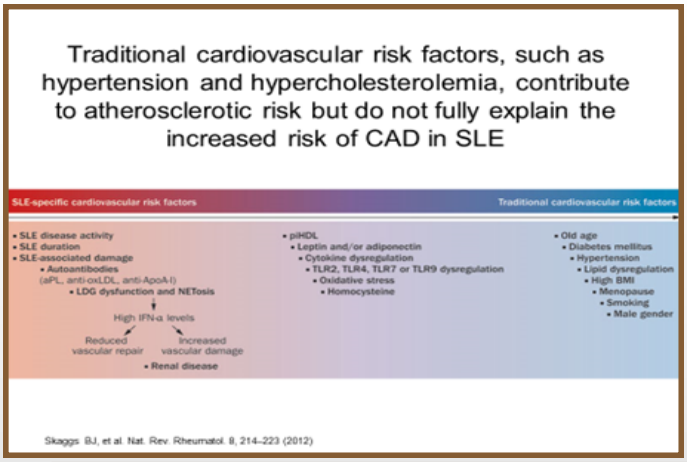
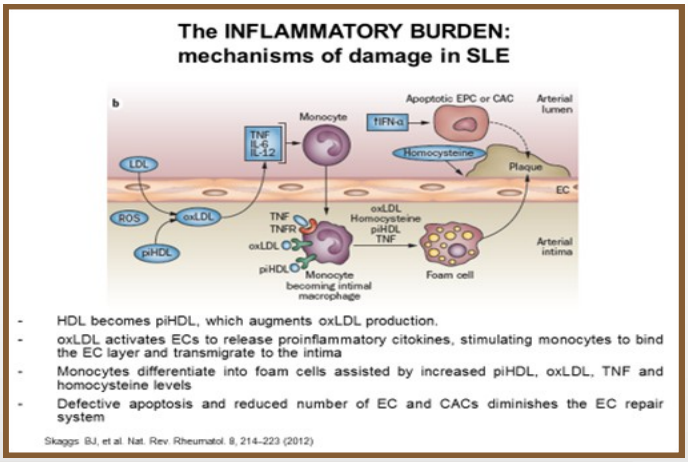
Atherosclerosis and Lupus

Giacomo Emmi
(Florence, Italy)

Dr. Giacomo Emmi from Florence spoke about the relationship existing between SLE and atherosclerosis. In patients suffering from SLE, the prevalence and the incidence of mortality due to cardiovascular disease increases, far more so in women than in men. In these patients, the prevalence of recurrence due to cardiovascular disease also increases. Among the risk factors, those most closely linked to SLE are the metabolic syndrome, the activity of the disease and the use of corticosteroids. These patients usually suffer from hyperdyslipidaemia, apart from which, they have altered lipoproteins and present pro-inflammatory HDLs. In pharmacological terms, hydrochlorochine seems to have a protective profile as far as the incidence of diabetes is concerned. Statins are election drugs in these patients, and even Vitamin D has a protective effect against the cardiovascular risk factors. From a pathogenetic point of view, the inflammatory condition seems to play a central role in determining cardiovascular risk. Another phenomenon that facilitates the onset of atherosclerosis is the formation of NETS, which are modified neutrophil granulocytes capable on one hand of "capturing" the endothelial cells and on the other, of modifying the HDLs and making them proatherogenic. In patients suffering from SLE there is also an immunity defined as "adaptive", characterised by the action of the anti-DNA antibodies that stimulate the interferon α which is in turn assigned the task of stimulating the T-lymphocytes which, by penetrating inside the vascular wall, give rise to the genesis of the atherosclerotic processes at the subintimal level. The speaker also described other pathogenetic proatherogenic mechanisms of the B-lymphocytes.





What are the main traditional risk factors for atherosclerosis in patients suffering from SLE? What is the weight of the activity of disease on the cardiovascular risk? What is the dyslipidaemic pattern in patients suffering from SLE? What is the optimal therapeutic protocol for reducing exposure to cardiovascular risk in patients suffering from SLE? What is the role of the innate immunity and acquired immunity in the determinism of exposure to cardiovascular risk in patients suffering from SLE?

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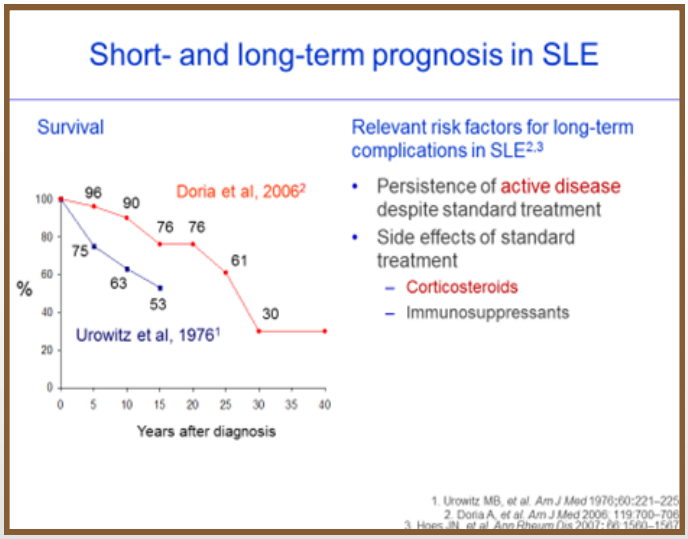
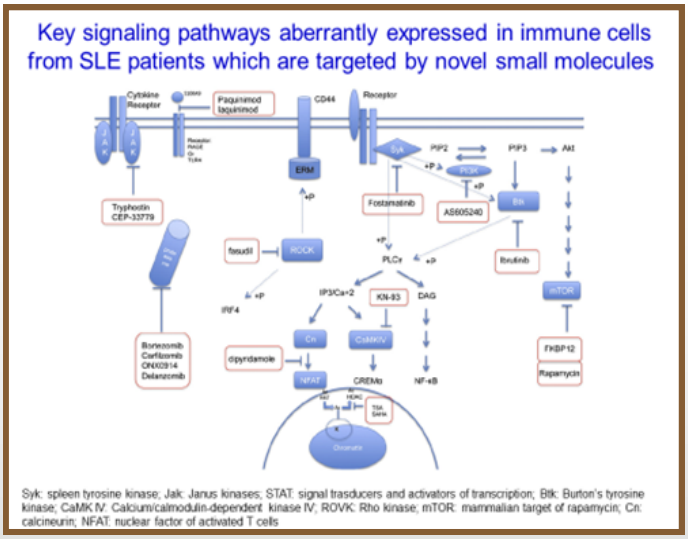
New therapeutic targets: from those biological to small molecules

Andrea Doria
(Padua, Italy)

Prof. Doria from Padua addressed this issue starting from the statement that over the course of the years, the long-term prognosis in patients suffering from SLE has improved considerably, despite still being at a severe level: 20% of patients die during the first 15-20 years of the disease. The most significant among the risk factors are the activity status of the disease and the adverse events linked to the pharmacological treatments such as the corticosteroids and immunosuppressant drugs. What must we do to respond to these still unresolved "needs"? The answer lies in the development of new drugs of a biological origin and inhibitors of the small molecules. As far as the drugs of a biological origin are concerned, the speaker presented an overview of the main molecules being studied starting from the key question: can the biological targets reduce the activity status of the disease and the dosage of cortisone so as to prevent the structural damage observed in patients suffering from SLE? Although there is a considerable number of biological drugs being studied, to date only one of these has been approved by the FDA and the EMA, namely, *Belimumab*. As regards the inhibitors of the small molecules, the speaker underscored how in patients suffering from SLE there is a whole series of outlier metabolic signals that manifest in the target immune cells of these small molecules, in turn the target of these new drugs. These inhibitors can be administered orally, unlike the biological ones, and they exploit multiple action mechanisms; consequently they seem to be generally more effective than the monoclonal antibodies.





What are the main biological drugs currently being studied? Is *Belimumab* a satisfactory drug for the treatment of SLE? What results have been obtained by the other monoclonal antibodies being studied? What are the main inhibitors of the small molecules under study? What are the results of the clinical trials currently underway?

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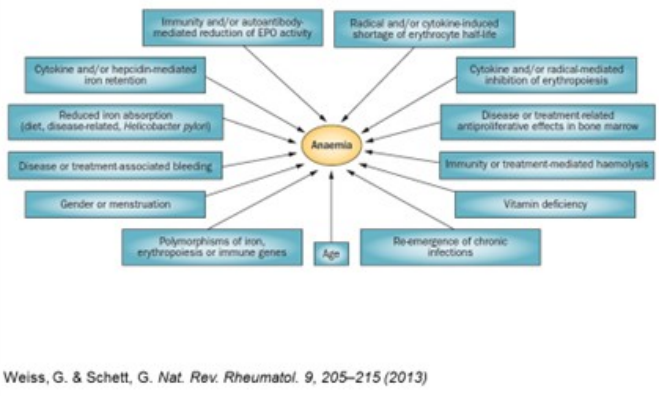
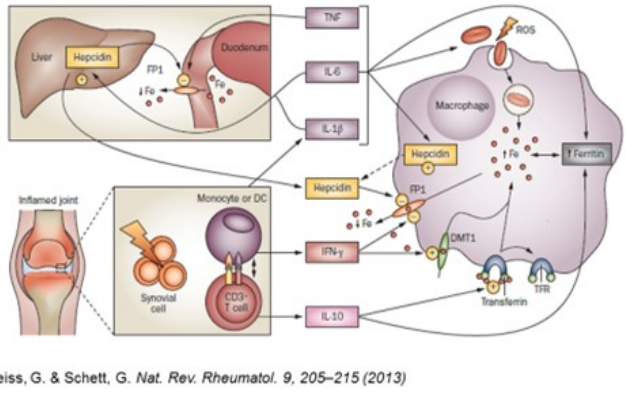
Haematological involvement in patients suffering from SLE

Lorenzo Emmi
(Florence, Italy)

Prof. Lorenzo Emmi spoke about the involvement of the haematic compartment in the pathogenetic processes of SLE. The main pathological conditions include haemolytic and non-haemolytic anaemia, leukopoenia, lymphocytopoenia, neutropoenia, thrombocytopoenia, thrombocytopoenic purpura and the macrophage activation syndrome. A basic picture of these patients is characterised by the presence of tendentially low levels of haemoglobin, in both men and women. This condition, associated with an increase in the reticulocytes, is able to provoke haemolysis and acute bleeding, while in the presence of a normal reticulocyte count there may be a situation of chronic anaemia and nutritional deficiencies of iron, folates, and Vitamin B12. The speaker then described these pathological cases. The second part of the presentation was dedicated to an analysis of the pharmacological treatments of the individual pathological conditions, such as haemolytic and non-haemolytic anaemia, the forms of anaemia present during chronic diseases, leukopoenia, lymphocytopoenia, neutropoenia, thrombocytopoenia, thrombocytopoenic purpura, and the macrophage activation syndrome.



Weiss, G. & Schett, G. *Nat. Rev. Rheumatol.* 9, 205–215 (2013)



Weiss, G. & Schett, G. *Nat. Rev. Rheumatol.* 9, 205–215 (2013)

What are the main haematological pathologies typical of patients suffering from SLE? Are the forms of haemolytic or non-haemolytic anaemia more frequent In patients with SLE? What percentage of patients suffer from anaemia during the course of chronic diseases? What are the main pharmacological products used during the treatment of thrombocytopenia?

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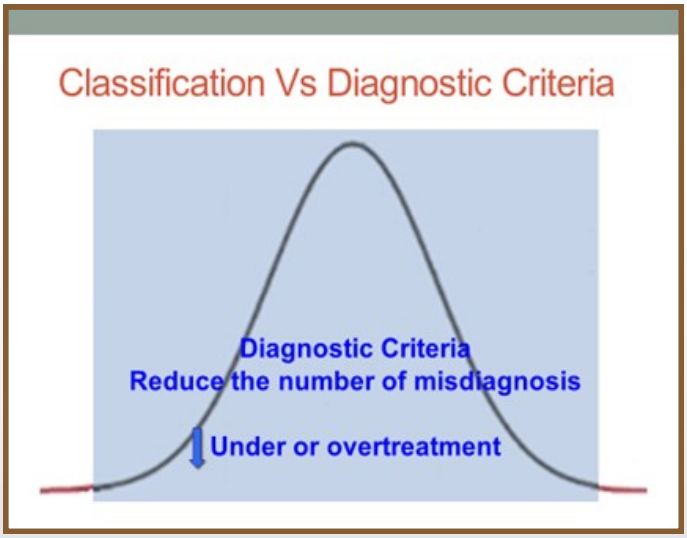
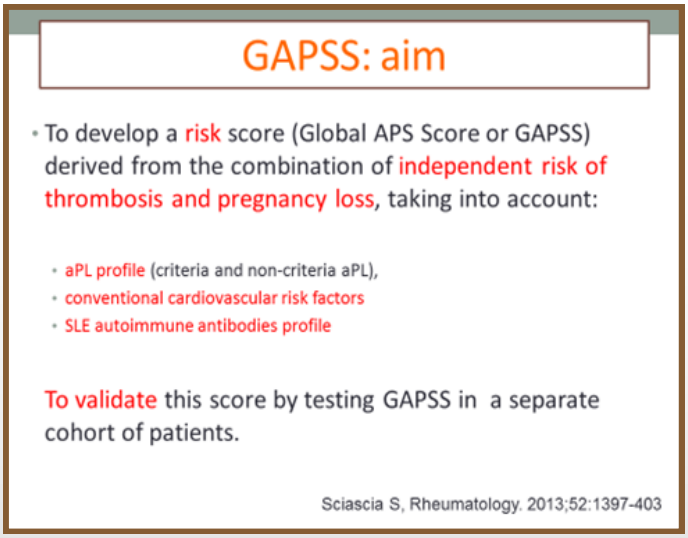
APS: diagnostic criteria and risk assessment

Savino Sciascia
(London, UK)

Dr. Sciascia from Turin spoke about the classification criteria of APS and specified that in actual fact they have been designed more for clinical trials than for diagnosis in a "real life" context". By applying the criteria identified in the consensus conferences held over recent years in Sapporo and Sydney, the results are discordant. These criteria are more useful for the standardisation of a population, in order to set specific clinical trials. In diagnostic terms, in clinical practice it is necessary to add further criteria dictated by the clinical management of the patient in order to better identify patients who are suffering from the disease. Among these factors, the speaker mentioned complete thrombophilia screening, the auto-antibody activity during autoimmune diseases, the presence of cardiovascular factors, and the presence of antiphospholipid antibodies (aLP). He then presented the data produced by his work team aimed at identifying a new diagnostic score called the "Global APS Score" (GAPSS). This new diagnostic model is characterised by the combination of the independent risk of thrombosis and spontaneous abortion in female patients in whom an analysis of the aLP profile is also conducted, as well as an analysis of the conventional cardiovascular risk factors and the profile of the autoimmune antibodies of SLE. The speaker then described the clinical trials that have given rise to the validation of the GAPSS.





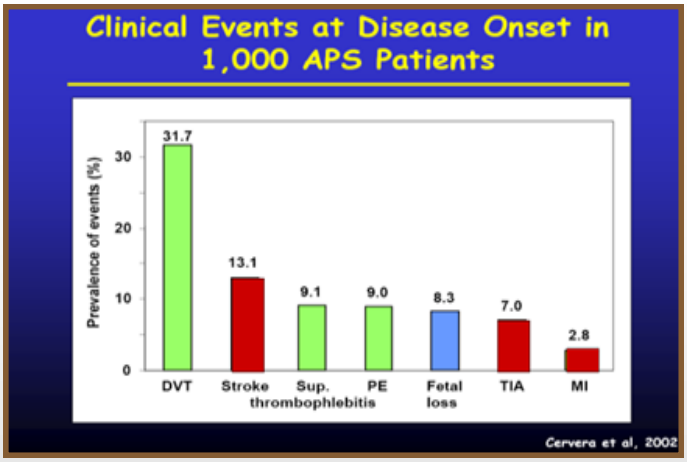
What are the main risk factors specifically for APS?
What studies have been conducted to validate the GAPSS?
What is the value of the GAPSS in close association with a high risk of recurrence of the disease?

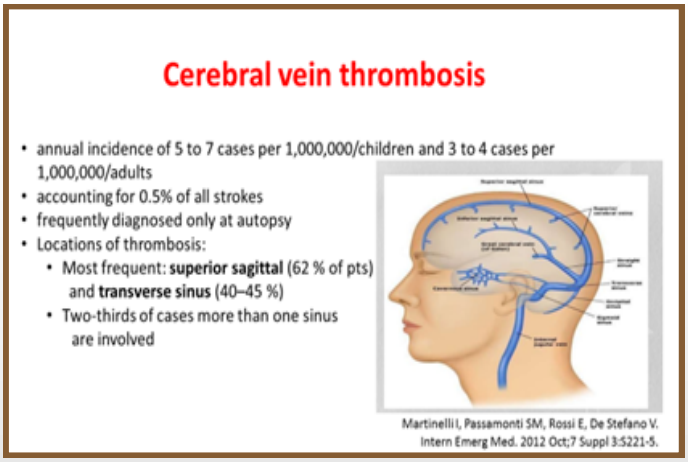
HIGHLIGHTS

Venous thromboembolism: diagnostic criteria and differential diagnosis during the course of APS

Domenico Prisco
(Florence, Italy)

Prof. Prisco from Florence spoke about venous thromboembolism, a clinical picture that is highly indicative of the presence of APS, especially in patients under the age of 50. More specifically, the speaker presented data on recurrent venous thrombosis, pulmonary embolism and the situations of thrombosis present in atypical sites, such as at a cerebral, mesenteric, and hepatic level and also during the Budd-Chiari syndrome. Deep vein thrombosis (DVT) is the thrombotic form with the highest prevalence during APS; in diagnostic terms, it is essential to proceed with an objective diagnosis in view of the high risk level to which these patients are exposed. Imaging helps with the diagnosis in only 10-25% of cases. Differential diagnosis may also be problematic due to the wide range of other pathologies that manifest similar signs and symptoms. The speaker analysed the criteria to be applied in case of a suspect diagnosis and described a useful diagnostic algorithm for identifying deep vein thrombosis. As far as the diagnosis of pulmonary embolism is concerned, the speaker pointed out how only in 10-20% of cases can this be confirmed, besides which, the same clinical presentation is also characterised by a high degree of variability and as a result, differential diagnosis is decidedly very complex. The speaker then described some forms of thrombosis located in common sites, with special focus on the extremely rare cerebral form that is more frequent in young women and characterised mainly by headaches. In the case of a deep vein thrombosis in a patient under the age of 50, in the absence of clear risk factors but with a previous diagnosis of SLE or other autoimmune diseases, and in case of a recurrence while under anticoagulant therapy, it is recommended to consider that APS could be the main cause of the DVT. In these patients it is necessary to carry out a screening in order to identify the antiphospholipid antibodies. The speaker concluded his talk with a description of a diagnostic algorithm based on the integration of the clinical assessment with the search for classical laboratory criteria.





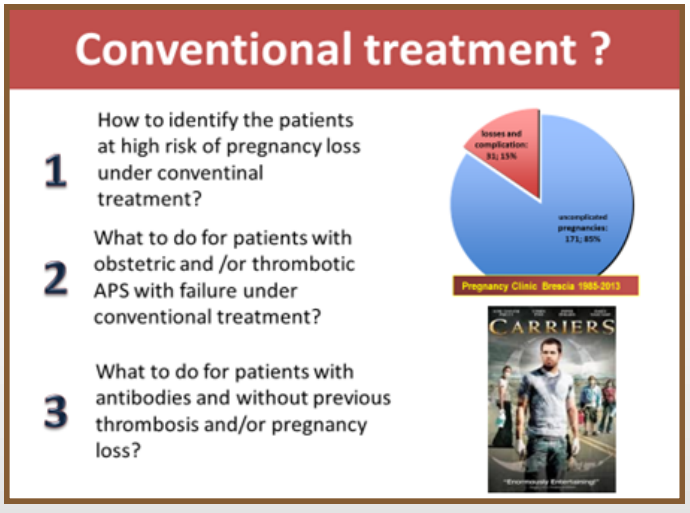
What are the main pathological pictures to be considered during the differential diagnosis of DVT? What are the key points of the diagnostic algorithm of DVT? What are the signs and symptoms observed in patients suffering from pulmonary embolism? What are the main pathological conditions to be considered during the differential diagnosis of pulmonary embolism? Which diagnostic tree should be applied in patients with suspected pulmonary embolism?

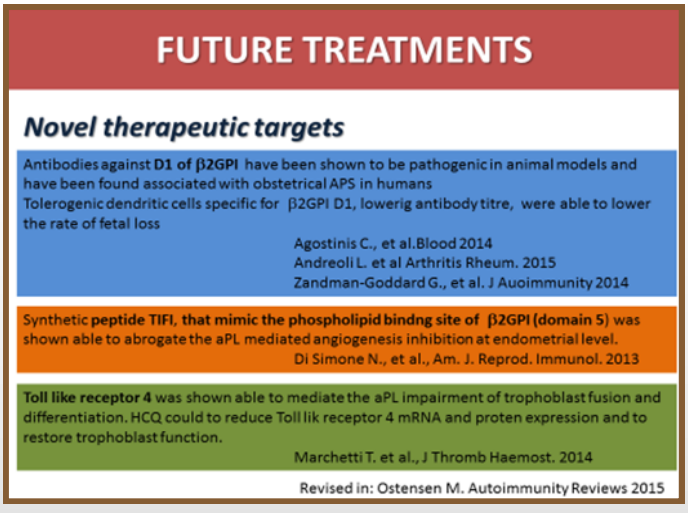
HIGHLIGHTS

Pregnancy and APS: management and treatment

Angela Tincani
(Brescia, Italy)

Prof. Tincani of Brescia spoke about the obstetric syndrome in patients suffering from APS. The pharmaceutical products normally used in the treatment of the obstetric syndrome are heparin and aspirin. For ensuring foetal survival, the best treatment consists of the combination of heparin and aspirin at low doses. This treatment has historically determined a significant improvement in the reduction of spontaneous abortions. Nevertheless, it has not completely overcome the problem, which stands at 30 % in women with spontaneous abortions despite the application of this therapeutic protocol. The speaker then went on to examine the possible predictive factors that are useful for identifying high-risk women and indicated the "triple antibody positivity" as the factor offering the highest risk predictability for spontaneous abortion. However, which treatments ensure the greatest help in these types of patients? Heparin-based treatment combined with aspirin must be completed with an additional association of other pharmaceutical products such as corticosteroids or hydroxychloroquine. There are also possible new therapeutic targets such as the anti-D1 or β2 GPI antibodies. Another new therapeutic target is represented by a synthetic peptide, known as TIFI, which mimes the phospholipidic receptor of β2 GPI. In the last part of her talk, the speaker addressed the issue of the treatment of patients with positive antibodies in the absence of spontaneous abortions or thrombotic-type symptoms. In fact, based on international criteria, these patients are not candidates for the classical pharmacological treatment. At this point, the speaker proposed an alternative therapeutic protocol.





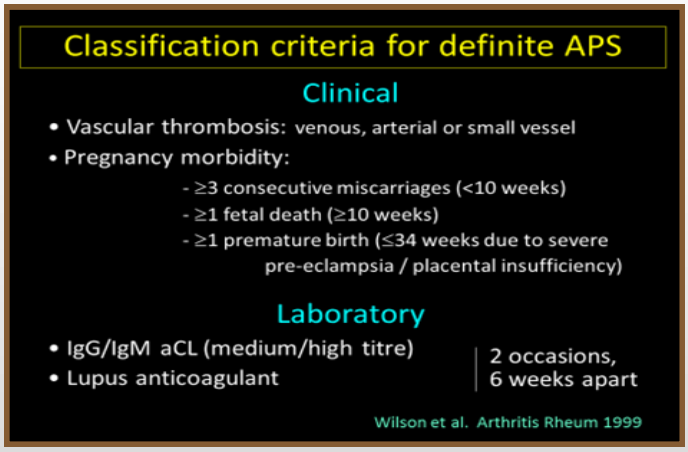
What are the clinical criteria for the diagnosis of the obstetric syndrome in patients suffering from APS? What are the laboratory criteria? Does treatment with aspirin and heparin protect women suffering from APS? Which treatment can be administered to patients with positive antibodies who have not had any abortions and who do not present any signs or symptoms of thrombosis?

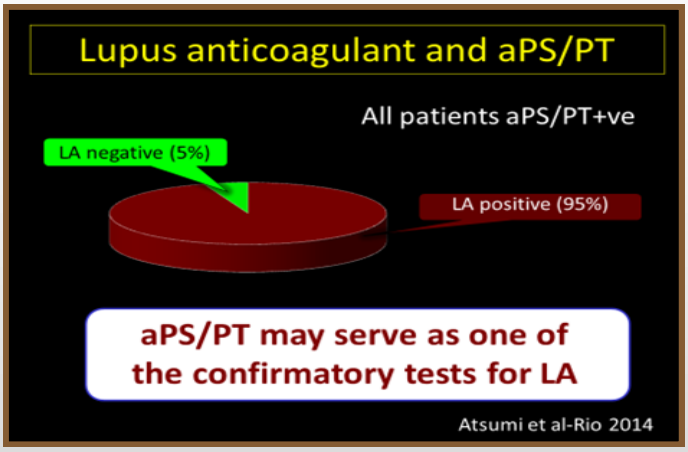
HIGHLIGHTS

The unresolved needs of patients suffering from APS today

Laura Bertolaccini
(London, UK)

Starting from the history of the diagnostic criteria applied in patients suffering from APS, Prof. Bertolaccini from London highlighted the main limits of the current diagnostic tools, while at the same time giving indications of the principal criteria potentially useful for making a diagnosis. Based on the data presented, she pointed out that the best tests currently available for identifying patients suffering from APS are the dosage of the anti-cardiolipin antibodies (aCL), anti β2 GPI antibodies and the lupus anticoagulant (LA). However, these tests are not able to identify the entire spectrum of APS markers. In addition, it is necessary to collect more data in order to enhance the standardisation of the anti β2 GPI immune tests. A new pathway that would allow for identifying patients suffering from APS is the application of the test for the antibodies towards Domain I of the β2 GPIs. Its positivity is associated with thrombotic phenomena and obstetric diseases, but even so, the data produced are still not sufficient for establishing its value as an independent risk factor. Other antibody tests, developed for diagnosing patients suffering from APS, include the dosage of the anti-prothrombin (aPT) and antiphosphatidylserine/prothrombin (aPS/PT) antibodies. The data produced from these tests have established their role as independent risk factors for thrombosis. Their use could therefore enhance the diagnostic predictability and the assessment of the thrombotic risk in patients suffering from APS. Another extremely important aid is the dosage of the antiphospholipid (aPL) antibodies: from the data presented by the speaker it is evident that these antibodies pass through the placenta and the encephalic barrier which therefore makes it possible for them to interfere with the cerebral development of the foetus. She then stressed the need to produce long-term data on children born of mothers in whom these antibodies are present. Another highly relevant aspect could be that of developing new therapeutic aids capable of competing with the aPL antibodies at the level of the target organs, in the aim of improving the outcome of patients in therapy who are suffering from APS.





What are the main steps in the history of the diagnosis of APSCome misurare l'attività infiammatoria nei processi di aterosclerosi? What are the classification criteria for the definition of APS? What is the predictive value of the anti- β2 GPI antibodies? What are the main tests for the dosage of aPL?

HIGHLIGHTS

These are some of the topics addressed during the congress works.
For a more in-depth analysis please visit the website of the Fondazione Internazionale Menarini which also contains the full version of the congress talks.

To follow the presentations of this convention just click on this link: www.fondazione-menarini.it/... and after having logged in, access the multimedia material.

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