II Congreso Panamericano de Espondiloartropatías

Conferencistas Invitados

Dr. Luis R. Espinoza
Profesor de Medicina; Jefe de la Sección de Reumatología Departamento de Medicina Interna, Louisiana State University School of Medicine, New Orleans, Estados Unidos de Norteamérica.

Conferencias: "Bases Infecciosas de las Artritis Reactivas"
"Terapia Biológica en Artritis Psoriásica. Experiencia con Agentes Anti-TNFα"

Dr. Anthony S. Russell
Profesor de Medicina Departamento de Medicina e Inmunología Universidad de Alberta, Edmonton, Canadá.

Conferencia: "Rol de las Drogas en las Espondiloartropatías en relación con los Riesgos Cardiovasculares"

Dr. Joachim Sieper
Profesor de Reumatología Free University; Profesor de Medicina y Reumatología, Benjamín Franklin University, Berlin, Alemania.

Conferencias: "Diagnóstico temprano de Espondilitis Anquilosante: de la sospecha a la confirmación".
"Terapia Biológica en Espondilitis Anquilosante"

Dr. David Yu
University of California Los Angeles, Estados Unidos de Norteamérica.

Conferencia: "Factores que estimulan la actividad promotora del HLA-B27"

Role of drugs in spondyloarthritis in relation to cardiovascular risks

Anthony S. Russell, MD

Dept. of Rheumatology, University of Alberta Hospital, Edmonton, Canada

Cardiovascular disease has long been considered as a disease of the vascular lumen but as intravascular ultrasound has emphasized, it is really a disease of the vessel wall. Thus the majority of myocardial infarctions occur in patients without prior significant arterial stenosis.

The underlying pathology is atheromatous plaque in the subendothelium of the vascular wall.

These plaques develop from a response to endothelial injury and are associated with chronic inflammation. The actin cytoskeleton plays an important role in the regulation of adhesion molecules that are expressed. Many signaling molecules in the actin filament can control local inflammation. Systemic markers of inflammation may better predict the risk for vascular events in inflammatory connective tissue diseases than do conventional coronary heart disease risk parameters. AS patients have an increase in overall mortality and "an excess mortality from circulatory disease has been quoted at 20 to 40%". Patients have significant increase in circulating IL 6, CRP, as well as vWF. Patients with rheumatoid arthritis and systemic lupus clearly have increased CHD risks but how far this is due to the use of steroids or to intrinsic parameters such as circulating immune complexes, is not clear. Steroids are rarely used in AS patients. The role of drugs both in changing risk parameters such as increasing oxidant stress, altering plasma homocysteine and endothelial cell function, as well as in affecting outcome will be reviewed.

Measurements of endothelial and vascular functions are now relatively noninvasive and even surrogates such as plasma E-selection may be appropriate: Whether anti TNF and agents will indeed be able to reverse what appears to be TNF induced impairment of vasodilation and whether this provides a further rationale for their use, is still uncertain.

Early diagnosis of ankylosing spondylitis: from suspicion to confirmation

Joachim Sieper, MD

Rheumatology, Charité, Berlin Germany

Ankylosing spondylitis is a relatively frequent disease with an assumed prevalence of between 0.2 and 0.8%. Furthermore, the disease normally starts early in life, normally in the 3. decade of life. Until now there is an unacceptably long delay between the occurrence of the first symptoms and making a final diagnosis of about 6-10 years. Early diagnosis has become more and more important because effective therapies have become available. There are two major reasons for such a delay of diagnosis: 1. The diagnosis still relies on the presence of chronic changes as detected by x-rays, however, it often takes several years of ongoing inflammation before such chronic changes become visible. 2. It is a major challenge for the primary care physician, who sees patients with chronic low back pain first, to identify spondyloarthritis as the cause of back pain. MRI has become an important tool for such an early diagnosis. We have recently proposed that an early diagnosis can reliably be made if several clinical, imaging and laboratory (HAL-B27) parameters are positive, even before the occurrence of x-rays changes. We have also proposed to use the presence of the clinical symptom of inflammatory back pain (morning stiffness with improvement by exercise) or a positive HLA-B27 testing as screening parameter for primary care physicians. In a first study in Germany, referral to a specialized rheumatology clinic using these screening parameters resulted in a diagnosis of axial spondyloarthritis in 46% of patients, 50% of these patients each with and without radiographic sacroiliitis. Thus, it can be expected for the near future that a diagnosis will be made earlier and patients will be treated earlier with specific therapies.

Biologic therapy of ankylosing spondylitis

Joachim Sieper, MD

Rheumatology, Charité, Berlin Germany

Recently, recommendations for the management of ankylosing spondylitis (AS) have been published by the 'Asessment in Ankylosing Spondylitis' (ASAS) working group and by EULAR. For the axial manifestations there are only two groups of effective drugs: the NSAIDs and the TNF-blocking agents. Patients who have active AS and had failed previous NSAIDs therapy are candidates for TNF-blocker therapy. Unlike rheumatoid arthritis, conventional DMARDs are not effective in AS. All three TNF-blocking agents, infliximab, etanercept, and adalimumab, induce a major improvement of the disease activity in about 50% of patients. Long-term follow-up indicates that the efficacy and side effects remain stable over several years, about a 10% drop-out rate can be expected every year. Extrarheumatic manifestations such uveitis, psoriasis, and inflammatory bowel disease occur in about 40% of AS patients. In general, the TNF-blocking agents are also effective for these manifestations although not all work equally well. Given the good clinical efficacy and the clear reduction of inflammatory lesions as shown by MRI, the questions comes up whether TNF-blockers can also inhibit osteoproliferative changes such a syndesmophytes. This will be discussed in the presentations. Finally, very new data will be presented showing that adalimumab is also very effective in patients with axial spondyloarthritis in the pre-radiographic phase.

Factors which drive the promoter activity of HLA-B27

David Yu, MD, PhD

University of California Los Angeles, USA.

HLA-B27, an allele of HLA-B, is commonly recognized as a gene which is responsible for the pathogenesis of ankylosing spondylitis. For a gene to be expressed as a protein, the first step is transcription at the level of the genomic DNA. This is controlled largely by the promoter region of the gene. Studies have showed that the promoter region of HLA class I alleles reside mostly in the first 300 bp 5' of the first ATG codon, known as 5'UTR (untranslated region). For HLA-B alleles, only that of HLA-B7 has been studied for binding to transcription factors.

In order to understand what factors drive the promoter activity of HLA-B27, the first step is to compare the sequence of 5'UTR of HLA-B27 to that of HLA-B7 and other HLA-B alleles. The sequences of a total of 54 HLA-B alleles are available in the IMGT/HLA electronic database. In this electronic study, we used the sequence of the HLA-B*270502 to compare to the other 53 HLA-B alleles in the database. This database contains the sequences of 3 subtypes of HLA-B27: B*2705, B*2706 and B*2732.

We discovered that there are only 6 alleles in which the 300 bp 5'UTR are identical in sequence to B*270502: B*2706, B*2732, B*18101, B*1803, B*1817N and B*370101. In other words, the 5'UTR of HLA-B27 is different from those of the studied HLA-B7 and 48 other alleles. The differences in number of bp vary from 3 to 21 of the 300 bp.

The only HLA-B allele which has been studied in terms of transcription factor binding is HLA-B7. The 5'UTR HLA-B7 contains several domains responsible for binding to transcription factors: κB1 plus κB2 forming the enhancer A domain, ISRE, the X1/X2, S and Y boxes, and also the TATA and CAAT boxes. The enhancer A domain and the ISRE domains are responsible for binding to NFκB and interferon activated transcription factors respectively. Our next step in analysis was to compare the sequences of these domains in HLA-B27 to that of HLA-B7 and other HLA-B alleles. Most remarkably, the sequences of the following domains are completely identical in all 54 HLA-B alleles: κB1, κB2, ISRE and TATA box. There are considerably differences among the following domains: X1/X2, S and CAAT boxes.

The above analysis indicates that the transcription binding sites in HLA-B alleles are extremely conserved as far as binding to NFκB and interferon activated transcription factors are concerned. Understanding which cytokines and factors of innate immunity can lead to enhancement of activities in these domains will be important for understanding what drive the promoter activity of HLA-B27.