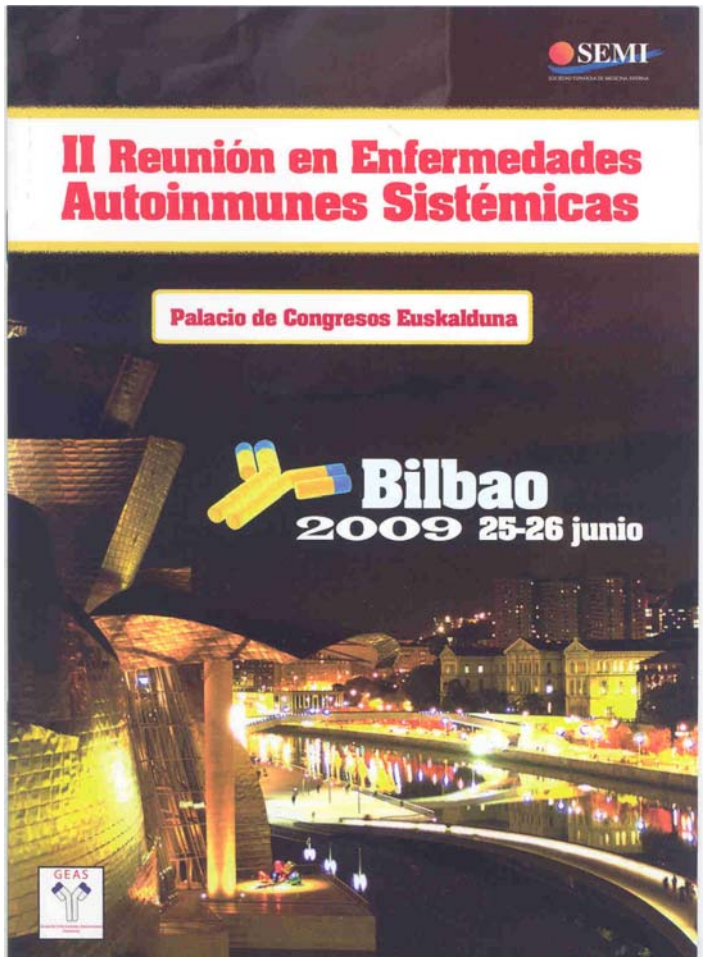
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Dr. Luis Caminal Montero
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09:00-09:20 h
Afección pulmonar en las miopatías inflamatorias
Dr. Albert Selva O'Callaghan
Unidad de Enfermedades Autoinmunes Sistémicas
Servicio de Medicina Interna
Hospital General Universitari Vall D´Hebrón. Barcelona
09:20-09:40 h
Significado clínico de los autoanticuerpos en las miopatías
Dr. Moisés Labrador Horrillo
Servicio de Medicina Interna
Hospital General Universitari Vall D´Hebrón. Barcelona
09:40-10:00 h
¿Existe la enfermedad mixta del tejido conectivo?
Dra. Mónica Ruiz Pombo
Servicio de Medicina Interna
Hospital San Rafael. Barcelona
10:00-10:15 h
Discusión
10:15-11:00 h
PRINCIPALES NOVEDADES EN ENFERMEDADES AUTOINMUNE
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Dr. Lucio Pallarés Ferreres
Unidad Enfermedades Autoinmunes Sistémicas
Servicio de Medicina Interna
Hospital Son Dureta. Palma de Mallorca
10:15-10:25 h
Lupus eritematoso sistémico
Dr. Juan Jiménez Alonso
Unidad de Enfermedades Autoinmunes Sistémicas
Servicio de Medicina Interna
Hospital Universitario Virgen de las Nieves. Granada
10:25-10:35 h
Síndrome antifosfolipídico
Dr. Guillermo Ruiz Irastorza
Servicio de Medicina Interna
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Cooney CM, Bruner GR, Aberle T, Namjou-Khales B, Myers LK, Feo L, Li S, D'Souza A, Ramirez A, Harley JB, Scofield RH.

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Cancro MP, D'Cruz DP, Khamashta MA.
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Garaud S, Le Dantec C, Jousse-Joulin S, Hanrotel-Saliou C, Saraux A, Mageed RA, Youinou P, Renaudineau Y.
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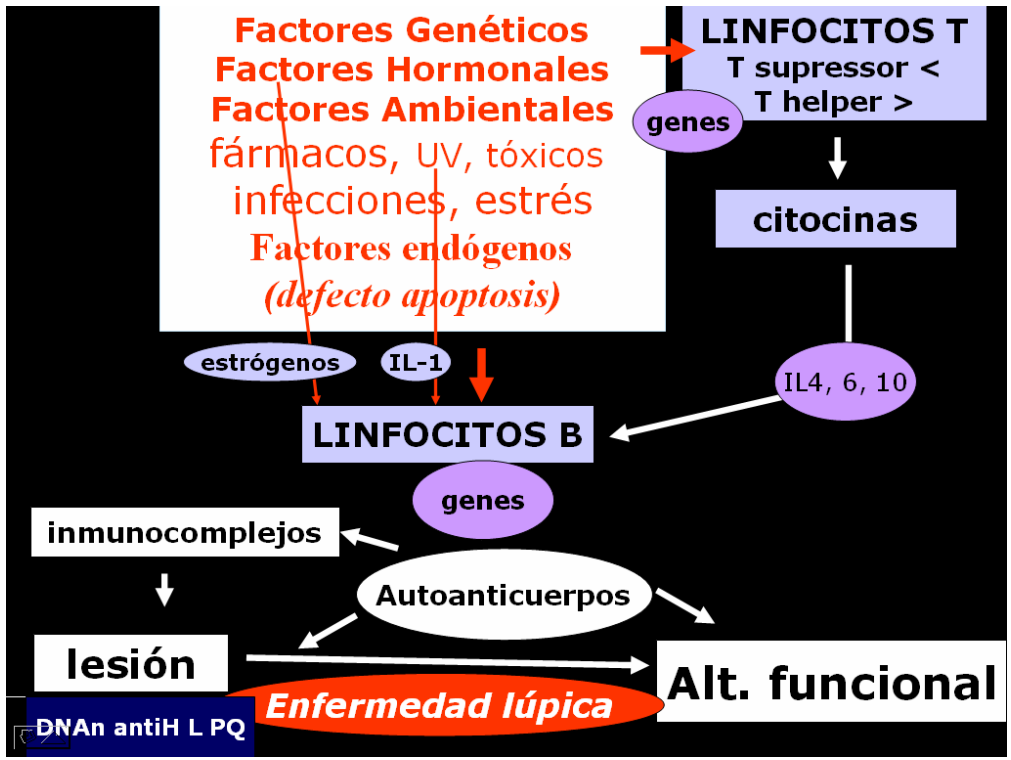

1: Arthritis Rheum. 2009 Apr 15;61(4):476-81.

Combined oral contraceptive use and the risk of systemic lupus erythematosus.

Bernier MO, Mikaeloff Y, Hudson M, Suissa S.

McGill Pharmacoepidemiology Research Unit, McGill University, Montreal, Quebec, Canada.

OBJECTIVE: To assess whether the risk of incident systemic lupus erythematosus (SLE) is associated with the use of combined oral contraceptives (COCs), because studies of the link between exogenous hormonal exposure and the risk of SLE have produced conflicting results. METHODS: We conducted a population-based nested case-control study among women ages 18-45 years, using the UK's General Practice Research Database. All incident cases of SLE from 1994-2004 (n = 786) were identified in the database and matched with up to 10 controls (n = 7,817) among women without SLE at the time of the case's diagnosis. RESULTS: The adjusted rate ratio (RR) of incident SLE associated with any use of COC was 1.19 (95% confidence interval [95% CI] 0.98-1.45), whereas with current use it was 1.54 (95% CI 1.15-2.07). The rate was particularly increased in current users who had only recently started COC use (RR 2.52, 95% CI 1.14-5.57) compared with longer-term current users (RR 1.45, 95% CI 1.06-1.99). The risk appeared to be particularly elevated with current exposure to first- or second-generation contraceptives (RR 1.65, 95% CI 1.20-2.26), and increasing with the dose of ethinyl estradiol (RR 1.42, 1.63, and 2.92 for < or =30 microg, 31-49 microg, and 50 microg, respectively). CONCLUSION: The use of COCs is associated with an increased risk of SLE. This risk is particularly elevated in women who recently started contraceptive use, suggesting an acute effect in a small subgroup of susceptible women.

1: Lupus. 2009 Apr;18(4):313-7.

Hormone replacement therapy in women with systemic lupus erythematosus and risk of cardiovascular disease.

Hochman J, Urowitz MB, Ibañez D, Gladman DD.

University of Toronto Lupus Clinic, Toronto Western Hospital, Toronto, Ontario, Canada.

We sought to determine the impact of hormone replacement therapy (HRT) on the occurrence of coronary artery disease (CAD) in women with systemic lupus erythematosus (SLE). Women in the University of Toronto lupus database who had taken HRT with no history of CAD were compared with all post-menopausal female patients with no history of HRT or CAD. Chi-squared and t-tests were used to compare the risk factors of CAD and Kaplan-Meier curve, log rank test and proportional hazard model with time-dependent covariates were used to compare the time from entry into the clinic to occurrence of CAD. A total of 114 HRT-user patients with no history of CAD were compared with 227 post-menopausal non-HRT user SLE controls. The groups were similar with respect to lupus anticoagulant, antiphospholipid antibody, cumulative steroid dose and classic cardiac risk factors. A similar percentage of patients developed CAD in the control (13.7%) and HRT (11.4%) groups. There was no difference in the time to development of CAD. In the multivariate analysis, HRT was not a risk factor for CAD. Only age (P = 0.0001, HR = 1.11, 95% CI = 1.05, 1.17) and SLEDAI-2K (P = 0.0001, HR = 1.10, 95% CI = 1.05, 1.16) were significantly associated with the risk of CAD. In this small group of patients with SLE, HRT alone did not appear to predispose to CAD.

1: Am J Pathol. 2008 Sep;173(3):600-9. Epub 2008 Aug 7.

Sex differences in autoimmune disease from a pathological perspective.

Fairweather D, Frisancho-Kiss S, Rose NR.

Department of Environmental Health Sciences, Bloomberg School of Public Health, Johns Hopkins University, 615 N. Wolfe St., Room E7628, Baltimore, MD 21205, USA. dfairwea@jhsph.edu

Autoimmune diseases affect approximately 8% of the population, 78% of whom are women. The reason for the high prevalence in women is unclear. Women are known to respond to infection, vaccination, and trauma with increased antibody production and a more T helper (Th)2-predominant immune response, whereas a Th1 response and inflammation are usually more severe in men. This review discusses the distribution of autoimmune diseases based on sex and age, showing that autoimmune diseases progress from an acute pathology associated with an inflammatory immune response to a chronic pathology associated with fibrosis in both sexes. Autoimmune diseases that are more prevalent in males usually manifest clinically before age 50 and are characterized by acute inflammation, the appearance of autoantibodies, and a proinflammatory Th1 immune response. In contrast, female-predominant autoimmune diseases that manifest during the acute phase, such as Graves' disease and systemic lupus erythematosus, are diseases with a known antibody-mediated pathology. Autoimmune diseases with an increased incidence in females that appear clinically past age 50 are associated with a chronic, fibrotic Th2-mediated pathology. Th17 responses increase neutrophil inflammation and chronic fibrosis. This distinction between acute and chronic pathology has primarily been overlooked, but greatly impacts our understanding of sex differences in autoimmune disease.

1: Arthritis Rheum. 2008 Aug;58(8):2511-7.

Klinefelter's syndrome (47,XXY) in male systemic lupus erythematosus patients: support for the notion of a gene-dose effect from the X chromosome.

Scofield RH, Bruner GR, Namjou B, Kimberly RP, Ramsey-Goldman R, Petri M, Reveille JD, Alarcón GS, Vilá LM, Reid J, Harris B, Li S, Kelly JA, Harley JB.

Oklahoma Medical Research Foundation, University of Oklahoma Health Sciences Center, and Oklahoma City VAMC, Oklahoma City, OK 73104, USA. hal-scofield@omrf.ouhsc.edu <hal-scofield@omrf.ouhsc.edu>

OBJECTIVE: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that predominantly affects women. Despite isolated reports of patients with coexisting Klinefelter's syndrome (47,XXY) and SLE, no association of Klinefelter's syndrome with SLE or any other autoimmune disease has been established. The present study was undertaken to investigate the prevalence of Klinefelter's syndrome in a large population of patients with SLE. METHODS: Sex chromosome genotyping was performed in 981 SLE patients, of whom 213 were men. A first group of 844 SLE patients from 378 multiplex families and a second group of 137 men with nonfamilial SLE were evaluated. In selected cases, chromosomes were enumerated by fluorescence in situ hybridization (FISH) and karyotyping in transformed B cell lines. RESULTS: Of 213 men with SLE, 5 had Klinefelter's syndrome (1 in 43). Four of them were heterozygous at X markers, and Klinefelter's syndrome was confirmed by FISH and karyotyping in the fifth. An overall rate of 47,XXY of 235 per 10,000 male SLE patients was found (95% confidence interval 77-539), a dramatic increase over the known prevalence of Klinefelter's syndrome in an unselected population (17 per 10,000 live male births). Asking men with SLE about fertility was highly sensitive (100%) for Klinefelter's syndrome. All 768 women with SLE were heterozygous at X. CONCLUSION: The frequency of Klinefelter's syndrome (47,XXY), often subclinical, is increased in men with SLE by approximately 14-fold compared with its prevalence in men without SLE. Diagnostic vigilance for 47,XXY in male patients with SLE is warranted. These data are the first to show an association of Klinefelter's syndrome with an autoimmune disease found predominantly in women. The risk of SLE in men with Klinefelter's syndrome is predicted to be similar to the risk in normal women with 46,XX and approximately 14-fold higher than in men with 46,XY, consistent with the notion that SLE susceptibility is partly explained by an X chromosome gene-dose effect.

1: Arthritis Rheum. 2008 Aug 15;59(8):1155-61.

Perinatal factors and adult-onset lupus.

Simard JF, Karlson EW, Costenbader KH, Hernán MA, Stampfer MJ, Liang MH, Mittleman MA.

Department of Epidemiology, Harvard University School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA. julia.simard@post.harvard.edu

OBJECTIVE: Some evidence suggests that perinatal factors, including birth weight and breastfeeding, may influence the occurrence of autoimmune rheumatic diseases. However, few studies have investigated these factors in patients with systemic lupus erythematosus (SLE). Therefore, we evaluated the role of birth weight, being breastfed, and preterm birth on the incidence of SLE in participants in the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHSII). METHODS: We studied 87,411 NHS participants and 98,413 NHSII participants without SLE at baseline who provided information on perinatal exposures. Among these women, during 26 (NHS) and 14 (NHSII) years of followup, 222 incident SLE cases were confirmed (136 NHS and 86 NHSII) by medical record review using American College of Rheumatology criteria. We used stratified Cox models to estimate the association of perinatal factors with SLE, adjusting for race, early passive cigarette smoke exposure, and parents' occupation. A random-effects meta-analysis was used to compute combined estimates across the 2 cohorts. RESULTS: After adjustment for multiple potential confounders, high birth weight (> or =10 pounds) was associated with increased rates of SLE compared with normal birth weight (7-8.5 pounds; rate ratio [RR] 2.7, 95% confidence interval [95% CI] 1.2-5.9), as was being born > or =2 weeks preterm (RR 1.9, 95% CI 1.2-3.0); however, being breastfed was not (RR 0.8, 95% CI 0.6-1.1). CONCLUSION: Birth weight > or =10 pounds and preterm birth were both positively associated with incident SLE among women.

1: Rheumatology (Oxford). 2008 Nov;47(11):1603-11. Epub 2008 Jul 8.

The genetics of SLE: an update in the light of genome-wide association studies.

Rhodes B, Vyse TJ.

Section of Molecular Genetics and Rheumatology, Division of Medicine, Imperial College London, London, UK.

Understanding the pathogenesis of SLE remains a considerable challenge. Multiple abnormalities of both the innate and adaptive immune system have been described and, furthermore, immunological dysfunction precedes clinical presentation by many years. There is a strong genetic basis to SLE, which means that genetic studies can play a key role in furthering our understanding of this disease. Since susceptibility variants are present from birth and are unaffected by the course of the disease, or by its treatment, genetic analysis is, perhaps uniquely, capable of identifying fundamental, causative, disease mechanisms. Over the last 12 months, there has been a staggering increase in our understanding of SLE genetics. We have seen the identification of new and important SLE susceptibility genes through candidate gene studies, and we have seen the publication of two whole-genome association analyses. The 'hypothesis free' whole-genome studies have provided additional evidence in support of a number of existing susceptibility genes and have identified novel gene candidates. In this article, we review the current SLE genetics literature in the light of these recent advances and we discuss our current understanding of the functional role of the key susceptibility genes. By considering how these genes fall into clusters with shared function we can begin to understand how dysregulation at a number of key immunological steps may predispose to the development of SLE.

1: Arthritis Rheum. 2008 Jul;58(7):1940-6.

Association of STAT4 with susceptibility to rheumatoid arthritis and systemic lupus erythematosus in the Japanese population.

Kobayashi S, Ikari K, Kaneko H, Kochi Y, Yamamoto K, Shimane K, Nakamura Y, Toyama Y, Mochizuki T, Tsukahara S, Kawaguchi Y, Terai C, Hara M, Tomatsu T, Yamanaka H, Horiuchi T, Tao K, Yasutomo K, Hamada D, Yasui N, Inoue H, Itakura M, Okamoto H, Kamatani N, Momohara S.

Tokyo Women's Medical University, Tokyo, Japan.

OBJECTIVE: STAT4 encodes a transcriptional factor that transmits signals induced by several key cytokines, and it might be a key molecule in the development of autoimmune diseases. Recently, a STAT4 haplotype was reported to be associated with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) in Caucasian populations. This was replicated in a Korean RA population. Interestingly, the degree of risk of RA susceptibility with the STAT4 haplotype was similar in the Caucasian and Korean populations. The present study was undertaken to investigate the effect of STAT4 on susceptibility to RA and SLE in the Japanese. METHODS: We performed an association study using 3 independent Japanese RA case-control populations (total 3,567 cases and 2,199 controls) and 3 independent Japanese SLE populations (total 591 cases). All samples were genotyped using the TaqMan fluorogenic 5' nuclease assay for single-nucleotide polymorphism (SNP) rs7574865, which tags the susceptibility haplotype. The association of the SNP with disease susceptibility in each case-control study was calculated using Fisher's exact test, and the results were combined, using the Mantel-Haenszel method, to obtain combined odds ratios (ORs). RESULTS: We observed a significant association of the

1: Transl Res. 2009 Jan;153(1):4-10. Epub 2008 Nov 14.

Comment in:
Transl Res. 2009 Feb;153(2):49-50.

Epigenetic regulation and the pathogenesis of systemic lupus erythematosus.

Pan Y, Sawalha AH.

Arthritis & Immunology Program, Oklahoma Medical Research Foundation, Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA.

The pathogenesis of systemic lupus erythematosus (SLE) is incompletely understood. Studies in both lupus animal models and human disease indicate a clear role for epigenetic defects, particularly DNA methylation, in the pathogenesis of lupus. T-cell DNA from active lupus patients is hypomethylated, which results in overexpression of methylation-regulated genes, T-cell autoreactivity, and autoimmunity in vivo. Inducing an extracellular signal-regulated kinase (ERK) signaling defect in T cells using a transgenic mouse model resulted in reduced DNA methyltransferase 1 (DNMT1) expression, overexpression of methylation-sensitive genes, and anti-double-stranded DNA (anti-dsDNA) antibody production. ERK signaling is known to be defective in lupus T cells, and this defect is now explained by impaired T-cell protein kinase C (PKC) delta activation. Herein, we discuss how defective epigenetic regulation is involved in the pathogenesis of lupus, which includes both DNA methylation and histone modification changes.

- **J Clin Invest. 2009 Apr;119(4):911-23. Multicéntrico internacional**
  - **Kallikrein genes are associated with lupus and glomerular basement membrane-specific antibody-induced nephritis in mice and humans.**
  - Liu K, Li QZ, Delgado-Vega AM, Abelson AK, Sánchez E, Kelly JA, Li L, Liu Y, Zhou J, Yan M, Ye Q, Liu S, Xie C, Zhou XJ, Chung SA, Pons-Estel B, Witte T, de Ramón E, Bae SC, Barizzone N, Sebastiani GD, Merrill JT, Gregersen PK, Gilkeson GG, Kimberly RP, Vyse TJ, Kim I, D'Alfonso S, Martin J, Harley JB, Criswell LA; Profile Study Group; Italian Collaborative Group; German Collaborative Group; Spanish Collaborative Group; Argentinian Collaborative Group; SLEGEN Consortium, Wakeland EK, Alarcón-Riquelme ME, Mohan C.
  - Collaborators (67)
  - Danieli MG, Galeazzi M, Querini PR, Migliaresi S, Scherbarth HR, Lopez JA, Motta EL, Gamron S, Drenkard C, Menso E, Allievi A, Tate GA, Presas JL, Palatnik SA, Abdala M, Bearzotti M, Alvarellos A, Caeiro F, Bertoli A, Paira S, Roverano S, Graf CE, Bertero E, Caprarulo C, Buchanan G, Guillerón C, Grimaudo S, Manni J, Catoggio LJ, Soriano ER, Santos CD, Prigione C, Ramos FA, Navarro SM, Berbotto GA, Jorfen M, Romero EJ, Garcia MA, Marcos JC, Marcos AI, Perandones CE, Eimon A, Battagliotti CG, Armadi-Simab K, Gross WL, Gromnica-Ihle E, Peter HH, Manger K, Schnarr S, Zeidler H, Schmidt RE, Ortego N, Callejas JL, Jiménez-Alonso J, Sabio M, Sánchez-Román J, Garcia-Hernandez FJ, Camps M, López-Nevot MA, González-Escribano MF, Harley JH, Riquelme MA, Kimberly R, Criswell L, Langefeld C, Tsao B, Jacob C

Kallikreins and lupus nephritis.

Ponticelli C, Meroni PL.

- The kidney kallikrein-kinin system plays important roles in inflammation, coagulation, angiogenesis, and regulation of vessel tone and permeability.
- In this issue of the JCI, Liu et al. provide data that suggest a protective role for kallikrein in animal models of anti-glomerular basement membrane(GBM) antibody-induced nephritis, an experimental model of Goodpasture disease (see the related article beginning on page 911).
- The authors suggest that kallikrein genes are involved in the development of SLE and lupus nephritis and may exert a renoprotective role.
- It is possible, however, that the kallikrein-kinin system may play dual roles: protecting the kidney against ischemia and interstitial fibrosis while also mediating vasodilation, inflammation, and activation of the innate immune response

1: Rheumatology (Oxford). 2008 Sep;47(9):1335-41. Epub 2008 Jul 23.

Active systemic lupus erythematosus is associated with failure of antigen-presenting cells to express programmed death ligand-1.

Mozaffarian N, Wiedeman AE, Stevens AM.

Seattle Children's Hospital Research Institute, 1900 Ninth Avenue, 7th floor, Seattle, WA 98101, USA. neely.mozaffarian@seattlechildrens.org

OBJECTIVE: Antigen-presenting cells (APC) play critical roles in establishing and maintaining peripheral tolerance. This is accomplished in part via expression of negative co-stimulatory molecules such as programmed death ligand-1 (PD-L1) on tolerogenic APC, such as immature myeloid dendritic cells (mDC). Several studies have strongly linked dysfunction of APC, including mDC, to the pathogenesis of SLE. The objective of this study was to determine whether APC expressed PD-L1 protein at normal levels during active lupus. METHODS: Peripheral blood mononuclear cells (PBMC) were isolated from 19 paediatric patients with SLE and from 17 healthy age-matched controls. PBMC from both cohorts were cultured in the absence of exogenously added stimuli, and leucocyte PD-L1 expression was measured by flow cytometry. RESULTS: Immature mDC and monocytes (Mo) from healthy children expressed little PD-L1 at initial isolation, but spontaneously up-regulated PD-L1 by 24 h. In contrast, both mDC and Mo from patients with active SLE failed to up-regulate PD-L1 over a 5 day time course, expressing this protein only during disease remissions. CONCLUSIONS: These data are the first to link active lupus with reversibly decreased PD-L1 expression on professional APC, suggesting a novel mechanism for loss of peripheral tolerance in SLE.

J Immunol. 2009 Apr 1;182(7):4167-74.

The cyclic AMP response element modulator {alpha} suppresses CD86 expression and APC function.

Ahlmann M, Varga G, Sturm K, Lippe R, Benedyk K, Viemann D, Scholzen T, Ehrchen J, Müller FU, Seidl M, Matus M, Tsokos GC, Roth J, Tenbrock K.

The cAMP response element modulator (CREM)alpha is a widely expressed transcriptional repressor that is important for the termination of the T cell immune response and contributes to the abnormal T cell function in patients with systemic lupus erythematosus

1: Arthritis Rheum. 2009 Feb;60(2):543-52.

Increased expression of CD40 on bone marrow CD34+ hematopoietic progenitor cells in patients with systemic lupus erythematosus: contribution to Fas-mediated apoptosis.

Pyrovolaki K, Mavroudi I, Sidiropoulos P, Eliopoulos AG, Boumpas DT, Papadaki HA.

University of Crete School of Medicine, Heraklion, Crete, Greece.

OBJECTIVE: Patients with systemic lupus erythematosus (SLE) display increased apoptosis of bone marrow (BM) CD34+ hematopoietic progenitor cells. This study was undertaken to evaluate the expression of CD40 and CD40L in the BM of SLE patients, and to explore the possible involvement of these molecules in apoptosis of CD34+ cells. METHODS: The proportion and survival characteristics of CD40+ cells within the BM CD34+ fraction from SLE patients and healthy controls were evaluated by flow cytometry. The production of CD40L by BM stromal cells was assessed using long-term BM cultures, and the effect of CD40L on the survival characteristics and clonogenic potential of CD34+ cells was evaluated ex vivo by flow cytometry and clonogenic assays. RESULTS: SLE patients displayed an increased proportion of CD40+ cells within the CD34+ fraction as compared with controls. The CD34+CD40+ subpopulation contained an increased proportion of apoptotic cells compared with the CD34+CD40- fraction in patients and controls, suggesting that CD40 is involved in the apoptosis of CD34+ cells. Stimulation of patients' CD34+ cells with CD40L increased the proportion of apoptotic cells and decreased the proportion of colony-forming cells as compared with untreated cultures. The CD40L-mediated effects were amplified following treatment with recombinant Fas ligand, suggesting that the effects of these ligands are synergistic. CD40L levels were significantly increased in long-term BM culture supernatants and adherent layers of BM cells from SLE patients as compared with controls. CONCLUSION: These data reveal a novel role for the CD40/CD40L dyad in SLE by demonstrating that up-regulation and induction of CD40 on BM CD34+ cells from patients with SLE contribute to the amplification of Fas-mediated apoptosis of progenitor cells.

Identification and characterization of a human CD5+ pre-naive B cell population. J Immunol. 2009;182:4116-26

Lee J, **Kuchen S**, **Fischer R**, **Chang S**, **Lipsky PE**. Seoul, Korea.

- We have identified a distinct pre-naive B cell population circulating in human peripheral blood that exhibits an intermediate phenotype between transitional and naive B cells
- CD5(+) pre-naive B cells show only partial responses to BCR stimulation and CD40 ligation and undergo more spontaneous apoptosis and cell death than do naive B cells
- capacity to differentiate into plasma cells and the ability to function as APCs.

1: Arthritis Rheum. 2008 Nov;58(11):3541-9.

Gene expression in systemic lupus erythematosus: bone marrow analysis differentiates active from inactive disease and reveals apoptosis and granulopoiesis signatures.

Nakou M, Knowlton N, Frank MB, Bertsias G, Osban J, Sandel CE, Papadaki H, Raptopoulou A, Sidiropoulos P, Kritikos I, Tassiulas I, Centola M, Boumpas DT.

University of Crete Medical School, Heraklion, Greece.

OBJECTIVE: The cells of the immune system originate from the bone marrow, where many of them also mature. This study was undertaken to examine gene expression in the bone marrow of patients with systemic lupus erythematosus (SLE), in order to better understand the aberrant immune response in this disease. METHODS: Bone marrow mononuclear cells (BMMCs) from 20 SLE patients (11 with active disease and 9 with inactive disease) and peripheral blood mononuclear cells (PBMCs) from 27 patients (16 with active disease and 11 with inactive disease) were studied; BMMCs and PBMCs from 7 healthy individuals and 3 osteoarthritis patients were studied as controls. Samples were analyzed on genome-scale DNA microarrays, with 21,329 genes represented. RESULTS: We identified 102 genes involved in various biologic processes that were differentially expressed between patient and control BMMCs; 53 of them are genes that are involved in major networks, including cell death, growth, signaling, and proliferation. Comparative analysis revealed 88 genes that were differentially expressed between bone marrow and blood, the majority of which are involved in cell growth and differentiation, cellular movement and morphology, immune response, and other hematopoietic cell functions. Unsupervised clustering of highly expressed genes revealed 2 major SLE patient clusters (active disease and inactive disease) based on gene expression in bone marrow, but not in peripheral blood. The up-regulated genes in the bone marrow of patients with active disease included genes involved in cell death and granulopoiesis. CONCLUSION: Microarray analysis of the bone marrow differentiated active from inactive SLE and provided further evidence of the role of apoptosis and granulocytes in the pathogenesis of the disease.

1: Arthritis Rheum. 2009 Jan;60(1):207-18.

Genetic, immunologic, and immunohistochemical analysis of the programmed death 1/programmed death ligand 1 pathway in human systemic lupus erythematosus.

Bertsias GK, Nakou M, Choulaki C, Raptopoulou A, Papadimitraki E, Goulielmos G, Kritikos H, Sidiropoulos P, Tzardi M, Kardassis D, Mamalaki C, Boumpas DT.

University of Crete Medical School, Heraklion, Crete, Greece.

OBJECTIVE: A putative regulatory intronic polymorphism (PD1.3) in the programmed death 1 (PD-1) gene, a negative regulator of T cells involved in peripheral tolerance, is associated with increased risk for systemic lupus erythematosus (SLE). We undertook this study to determine the expression and function of PD-1 in SLE patients. METHODS: We genotyped 289 SLE patients and 256 matched healthy controls for PD1.3 by polymerase chain reaction-restriction fragment length polymorphism analysis. Expression of PD-1 and its ligand, PDL-1, was determined in peripheral blood lymphocytes and in renal biopsy samples by flow cytometry and immunohistochemistry. A crosslinker of PD-1 was used to assess its effects on anti-CD3/anti-CD28-induced T cell proliferation and cytokine production. RESULTS: SLE patients had an increased frequency of the PD1.3 polymorphism (30.1%, versus 18.4% in controls; P=0.006), with the risk A allele conferring decreased transcriptional activity in transfected Jurkat cells. Patients homozygous for PD1.3-but not patients heterozygous for PD1.3-had reduced basal and induced PD-1 expression on activated CD4+ T cells. In autologous mixed lymphocyte reactions (AMLRs), SLE patients had defective PD-1 induction on activated CD4+ cells; abnormalities were more pronounced among homozygotes. PD-1 was detected within the glomeruli and renal tubules of lupus nephritis patients, while PDL-1 was expressed by the renal tubules of both patients and controls. PD-1 crosslinking suppressed proliferation and cytokine production in both normal and lupus T cells; addition of serum from patients with active SLE significantly ameliorated this effect on proliferation. CONCLUSION: SLE patients display aberrant expression and function of PD-1 attributed to both direct and indirect effects. The expression of PD-1/PDL-1 in renal tissue and during AMLRs suggests an important role in regulating peripheral T cell tolerance.

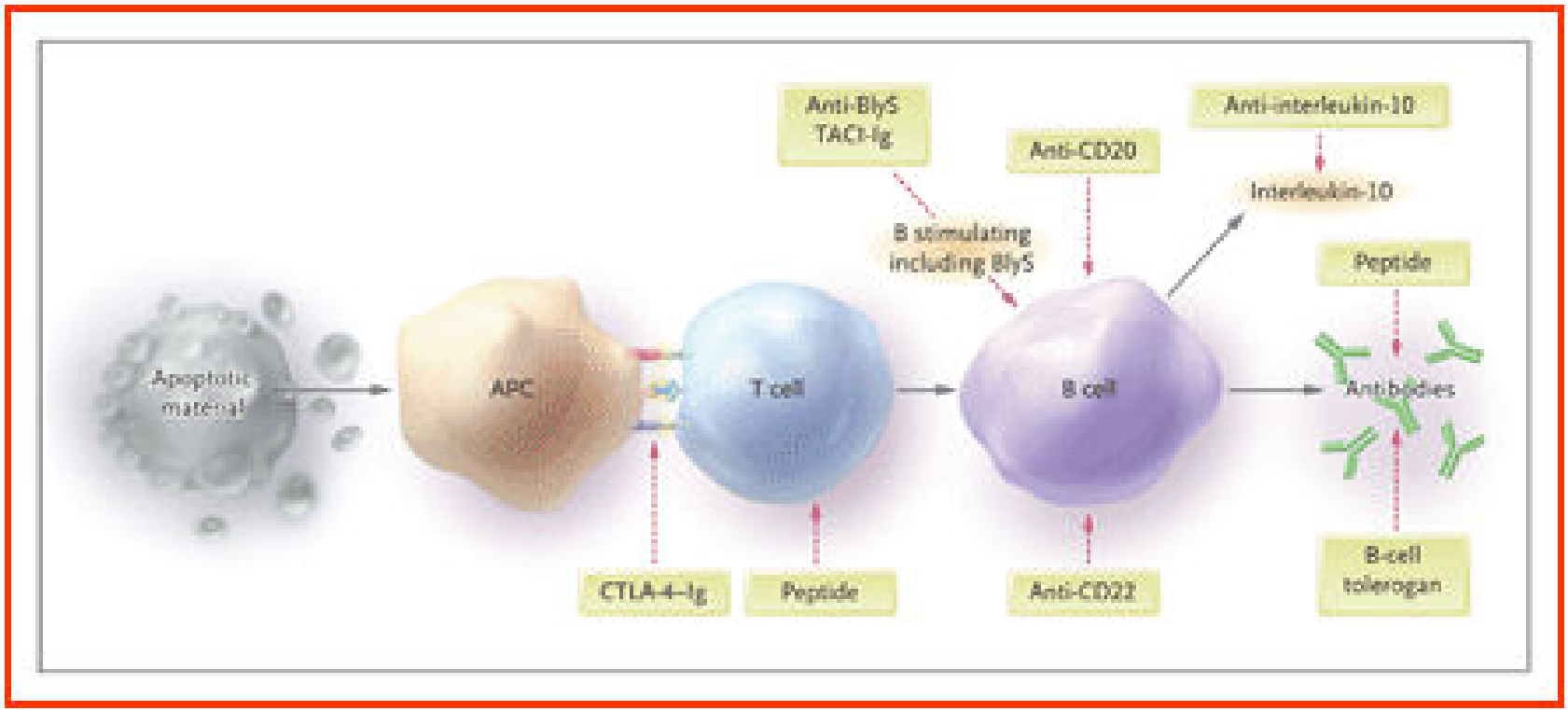

Figure 4. Targeted Therapeutic Approaches in Systemic Lupus Erythematosus.

This simplified diagram, which is based on our increased understanding of the im
therapeutic interventions. APC denotes antigen-presenting cell, BLyS B-lympho
and TACI-Ig transmembrane activator and CAML interactor immunoglobulin (C

1: J Immunol. 2008 Aug 1;181(3):2211-9.

Excessive production of IFN-gamma in patients with systemic lupus erythematosus and its contribution to induction of B lymphocyte stimulator/B cell-activating factor/TNF ligand superfamily-13B.

Harigai M, Kawamoto M, Hara M, Kubota T, Kamatani N, Miyasaka N.

Department of Pharmacovigilance, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan. mharigai.mpha@tmd.ac.jp

Expression and immunological significance of IFN-gamma, a pivotal cytokine in murine lupus, have not been clearly demonstrated in human systemic lupus erythematosus (SLE). In the present study we investigated the expression of IFN-gamma in peripheral blood T cells from patients with SLE and its role in the production of the soluble B lymphocyte stimulator (sBLyS). Peripheral blood T cells from patients with SLE expressed significantly larger amounts of IFN-gamma in response to stimulation with anti-CD3 mAb plus anti-CD28 mAb than those from normal controls as shown by three analytical methods, including ELISA, flow cytometry, and quantitative RT-PCR. The ratio of IFN-gamma-producing T cells to effector memory T cells in CD3(+)CD4(+) and CD3(+)CD8(+) populations in patients with SLE was significantly higher than that of normal controls. The T-box expressed in T cells (T-bet) mRNA/GATA-binding protein-3 (GATA-3) mRNA ratio was significantly higher in patients with SLE than in normal controls. T cell culture supernatants from patients with SLE contained significantly higher sBLyS-inducing activity than normal controls; this was almost completely inhibited by the addition of anti-human IFN-gamma mAb. Percentages of BLyS-expressing peripheral blood monocytes in patients with SLE were significantly higher than those of normal controls. Monocytes from patients with SLE produced significantly larger amounts of sBLyS in response to IFN-gamma than those from normal controls. Taken together, these data strongly indicate that the overexpression of IFN-gamma in peripheral blood T cells contributes to the immunopathogenesis of SLE via the induction of sBLyS by monocytes/macrophages, which would promote B cell activation and maturation.

1: J Clin Invest. 2009 May;119(5):1066-73. doi: 10.1172/JCI38010. Epub 2009 May 1.

The role of B lymphocyte stimulator (BLyS) in systemic lupus erythematosus.

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SLE, a chronic, multisystem autoimmune disorder with a broad range of symptoms, involves defective B cell selection and elimination of self-reactive B cells. B lymphocyte stimulator (BLyS), a soluble ligand of the TNF cytokine family, is a prominent factor in B cell differentiation, homeostasis, and selection. BLyS levels affect survival signals and selective apoptosis of autoantibody-producing B cells. High levels of BLyS may relax B cell selection and contribute to autoantibody production, exacerbating the SLE disease state. This review discusses the mechanism of BLyS action on B cells, its role in SLE, and specific targeting of BLyS in the treatment of SLE.

1: Lupus. 2009;18(6):556-60.

Ultraviolet light output of compact fluorescent lamps: comparison to conventional incandescent and halogen residential lighting sources.

Nuzum-Keim A, Sontheimer R.

University of Oklahoma College of Medicine, Oklahoma City, Oklahoma, USA.

Patients with photosensitive dermatologic and systemic diseases often question the ultraviolet light (UVL) output of household lighting sources. Such individuals have increasing concern about potential UVL exposure from energy-efficient compact fluorescent lamps (CFL), as little data have been presented concerning their UVL output. The objective was to compare, via pilot study, the levels of ultraviolet A (UVA) and ultraviolet B (UVB) leak between residential lighting sources. Equivalent wattage CFL, incandescent and halogen bulbs were purchased from local retailers in Oklahoma City, Oklahoma, USA. The UVA and UVB outputs of these sources were measured under controlled conditions at 10, 25, 50, 100 and 150 cm away from the light source using an IL-1700 research radiometer equipped with UVA and UVB detectors. Negligible UVB and UVA was detected at 100 and 150 cm. Therefore, data were analysed from measurements at 10, 25 and 50 cm only. The results demonstrated UVA leak highest from incandescent and halogen bulbs, and UVB leak highest from CFL. The overall UVA/UVB leak was lowest from CFL shielded during the manufacturing process. In conclusion, patients with photosensitivity have choices depending on their relative risk from different UVL wavelength spectra. UVB exposure risk may be reduced the greatest by utilising CFL with manufacturer-provided shields.

1: Lupus. 2009;18(7):630-638.

Cigarette smoking, N-acetyltransferase 2 polymorphisms and systemic lupus erythematosus in a Japanese population.

Kiyohara C, Washio M, Horiuchi T, Tada Y, Asami T, Ide S, Takahashi H, Kobashi G; The Kyushu Sapporo SLE (KYSS) Study Group.

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Cigarette smoking may be associated with an increased risk of systemic lupus erythematosus (SLE), but the underlying mechanism of this association remains unclear. N-acetyltransferase 2 (NAT2) is highly variable and detoxifies aromatic amines, an important class of carcinogens in tobacco smoke. Individuals who possess homozygous polymorphic alleles have a slower rate of metabolic detoxification of aromatic amines. We investigated the relationship of the NAT2 polymorphism to the risk of SLE with special reference to the interaction with cigarette smoking among 152 SLE cases and 427 controls in a female Japanese population. NAT2(*)4, NAT2(*)5B, NAT2(*)6A and NAT2(*)7B alleles were detected with polymerase chain reaction-restriction fragment length polymorphism. Individuals carrying the (*)4/(*)4 genotype are rapid acetylators, whereas those with homozygous non-(*)4 genotypes have a slow acetylator phenotype. Cigarette smoking was associated with an increased risk of SLE (odds ratio [OR] = 2.26; 95% confidence interval [CI] = 1.46-3.50). The slow acetylator genotype of NAT2 was significantly associated with an increased risk of SLE (OR = 2.34, 95% CI = 1.21-4.52) compared with the rapid acetylator genotype. A gene-environment interaction was suggested, with a combination of the NAT2 slow acetylator genotype and smoking conferring significantly higher risk (OR = 6.44, 95% CI = 3.07-13.52; attributable proportion due to interaction = 0.50, 95% CI = 0.12-0.88), compared with the NAT2 rapid acetylator genotype and no history of smoking. This study suggests that, in this Japanese population, the NAT2 slow acetylator status may be a determinant in susceptibility to SLE.

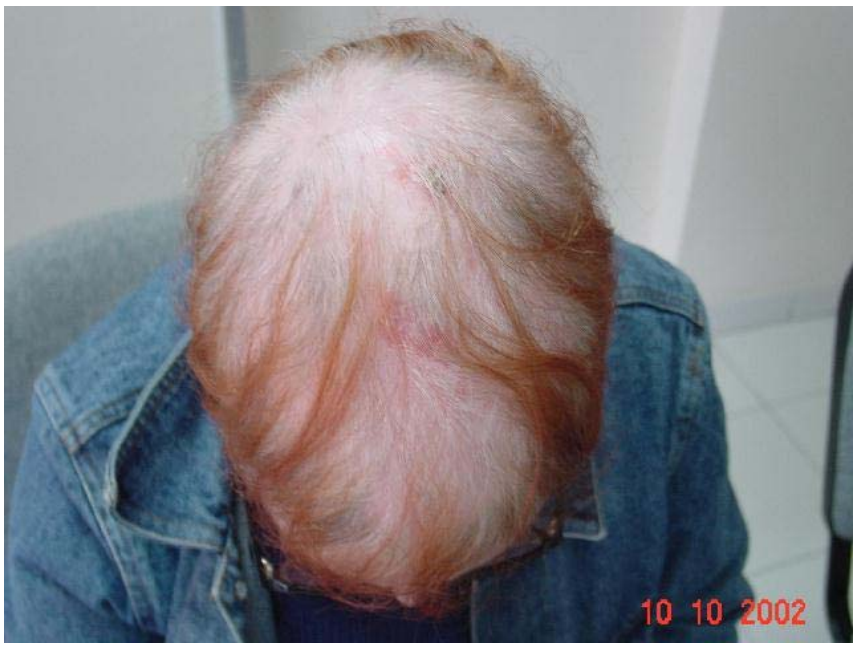
1: Lupus. 2009 Apr;18(4):318-31.

Severe tissue trauma triggers the autoimmune state systemic lupus erythematosus in the MRL/++ lupus-prone mouse.

Anam K, Amare M, Naik S, Szabo KA, Davis TA.

Regenerative Medicine Department, Naval Medical Research Center, Silver Spring, Maryland, USA.

Tissue damage associated with a severe injury can result in profound inflammatory responses that may trigger autoimmune development in lupus-prone individuals. In this study, we investigated the role of a large full-thickness cutaneous burn injury on the early onset of autoimmune disease in lupus-prone MRL/++ mice. MRL/++ mice (chronic model) exhibit autoimmune symptoms at >70 weeks of age, whereas MRL/-Fas(lpr) mice (acute model) develop autoimmune disease in 17-22 weeks due to a lymphoproliferative mutation. Autoimmune disease developed in MRL/++ mice (4-15 weeks post injury) is manifested by skin lesions, vasculitis, epidermal ulcers, cellular infiltration, splenomegaly, lymphadenopathy, hypergammaglobulinemia, elevated autoantibodies and renal pathologies including proteinuria, glomerulonephritis and immune complex deposition; complications that contribute to reduced survival. Transcription studies of wound margin tissue show a correlation between the pathogenic effects of dysregulated IL-1beta, IL-6, TNF-alpha and PGE(2) synthesis during early wound healing and early onset of autoimmune disease. Interestingly, MRL/++ mice with healed wounds (30-40 days post burn) strongly rejected skin isografts. Conversely, skin isografts transplanted onto naive age-matched MRL/++ littermates achieved long-term survival. Collectively, these findings suggest that traumatic injury exacerbates inflammatory skin disease and severe multi-organ pathogenesis in lupus-prone mice.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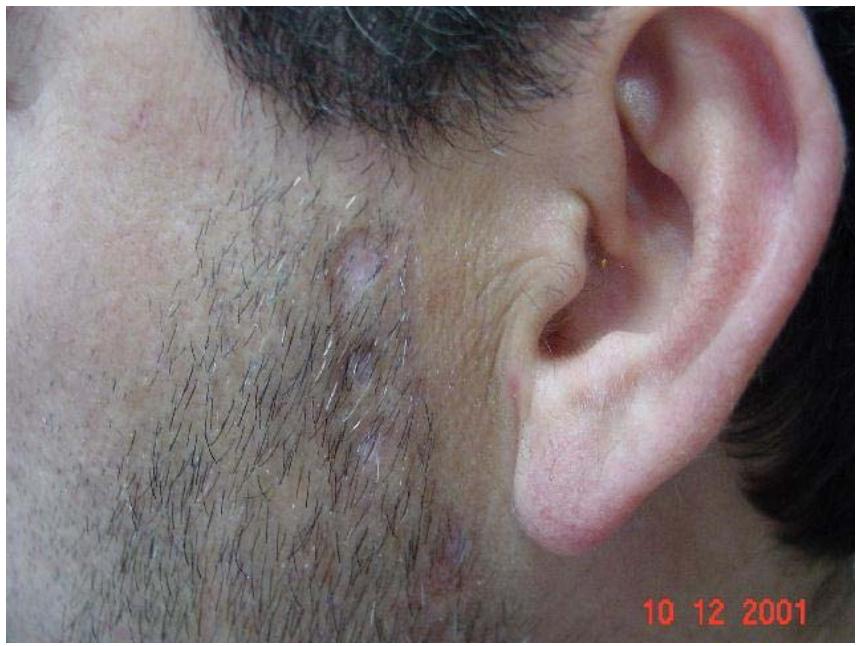
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Arch Dermatol. 2009 Mar;145(3):316-9.

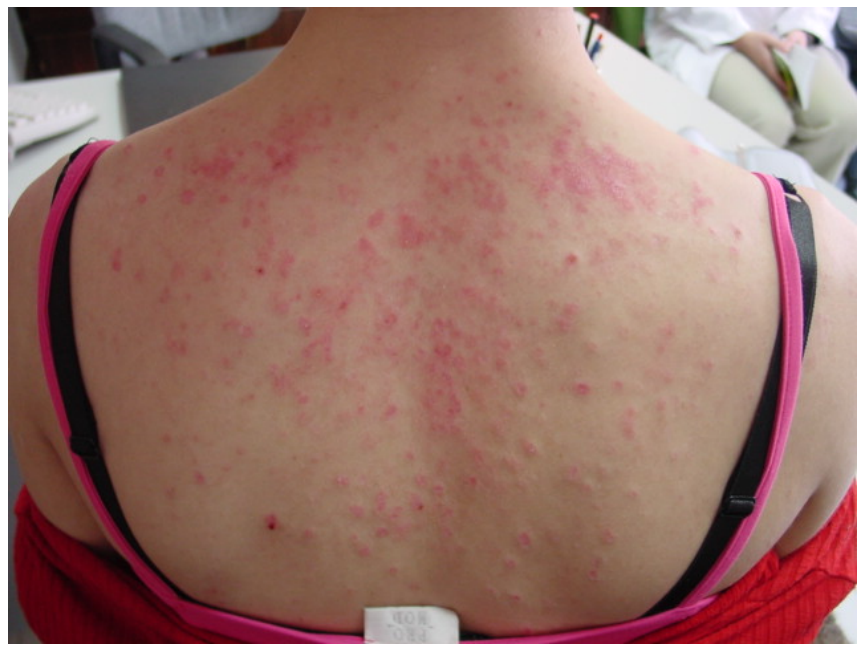
Incidence of cutaneous lupus erythematosus, 1965-2005: a population-based study.

Durosaro O, Davis MD, Reed KB, Rohlinger AL.

- A total of 156 patients with newly diagnosed CLE (100 females and 56 males) were identified between 1965 and 2005
- Nineteen patients with CLE had disease progression to SLE: cumulative incidence at 20 years, 19%; mean (SD) length to progression, 8.2 (6.3) years.

Kieffer C, et al. Strasbourg, France.
Neutrophilic urticarial dermatosis: a variant of neutrophilic urticaria strongly associated with systemic disease. Report of 9 new cases
Medicine (Baltimore). 2009 Jan;88(1):23-31.

Seven patients had associated systemic diseases: adult-onset Still disease (3 patients), systemic lupus erythematosus (3 patients), and Schnitzler syndrome (1 patient).



1: Arthritis Rheum. 2008 Sep 15;59(9):1332-40.

Features associated with, and the impact of, hemolytic anemia in patients with systemic lupus erythematosus: LX, results from a multiethnic cohort.

Durán S, Apte M, Alarcón GS, Marion MC, Edberg JC, Kimberly RP, Zhang J, Langefeld CD, Vilá LM, Reveille JD; Lumina Study Group.

University of Alabama at Birmingham, AL, USA.

OBJECTIVE: To examine the clinical and genetic correlates of hemolytic anemia and its impact on damage accrual and mortality in systemic lupus erythematosus (SLE) patients. METHODS: SLE patients (American College of Rheumatology [ACR] criteria) of Hispanic (Texan or Puerto Rican), African American, and Caucasian ethnicity from the LUMINA (LUpus in MInorities, NAture versus nurture) cohort were studied. Hemolytic anemia was defined as anemia with reticulocytosis (ACR criterion). The association between degrees of hemolytic anemia and socioeconomic/demographic, clinical, pharmacologic, immunologic, psychological, and behavioral variables was examined by univariable and multivariable (proportional odds model) analyses. Genetic variables (FCGR and Fas/Fas ligand polymorphisms) were examined by 2 degrees of freedom test of association and Cochran-Armitage trend tests. The impact of hemolytic anemia on damage accrual and mortality was examined by multivariable linear and Cox regression analyses, respectively. RESULTS: Of 628 patients studied, 90% were women, 19% were Texan Hispanic, 16% were Puerto Rican Hispanic, 37% were African American, and 28% were Caucasian. Sixty-five (10%) patients developed hemolytic anemia at some time during the disease course, 83% at or before diagnosis. Variables independently associated with degrees of hemolytic anemia were African American ethnicity, thrombocytopenia, and the use of azathioprine. Hemolytic anemia was associated with damage accrual after adjusting for variables known to affect this outcome; however, hemolytic anemia was not associated with mortality. CONCLUSION: The association of hemolytic anemia with thrombocytopenia suggests a common mechanism in their pathophysiology. Hemolytic anemia is an early disease manifestation and is associated with African American ethnicity and the use of azathioprine; it appears to exert an impact on damage but not on mortality.

1: Arthritis Rheum. 2009 Jan;60(1):199-206.

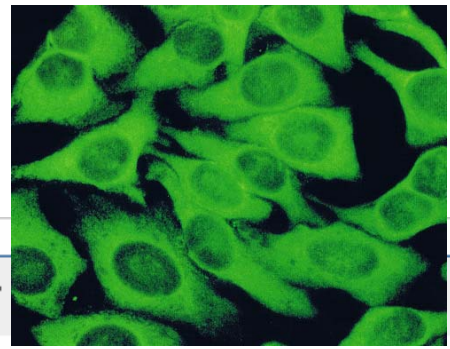
CXCR3+CD4+ T cells are enriched in inflamed kidneys and urine and provide a new biomarker for acute nephritis flares in systemic lupus erythematosus patients.

Enghard P, Humrich JY, Rudolph B, Rosenberger S, Biesen R, Kuhn A, Manz R, Hiepe F, Radbruch A, Burmester GR, Riemekasten G.

Charité University Hospital, Berlin, Germany. philipp.enghard@charite.de

OBJECTIVE: The high frequency of CD4+ T cells in interstitial infiltrates of patients with lupus nephritis suggests a contribution of these cells to local pathogenesis. The aim of this study was to examine the role of CXCR3 and the chemokine CXCL10 in recruiting these cells into the kidney and to determine whether the infiltrating T cells could be monitored in the urine to provide a reliable biomarker for acute lupus nephritis. METHODS: The frequencies of CD3+ T cells, CXCR3+ cells, and CXCL10+ cells were determined by immunohistochemical and immunofluorescence analyses of kidney sections from 18 patients with lupus nephritis. The frequency of CXCR3+CD4+ T cells was determined by flow cytometry of peripheral blood and urine from 38 patients with systemic lupus erythematosus (SLE), and the values were compared with disease activity as determined by the Systemic Lupus Erythematosus Disease Activity Index. RESULTS: In renal biopsy tissues from patients with lupus nephritis, a mean of 63% of the infiltrating cells expressed CXCR3, approximately 60% of them were T cells, and the CXCR3+ cells colocalized with CXCL10-producing cells. In biopsy tissues from SLE patients with acute nephritis, approximately 50% of the urinary CD4+ T cells were CXCR3+, as compared with 22% in the peripheral blood, and the frequency of urinary CXCR3+CD4+ T cells correlated with disease activity. Moreover, the number of urinary CD4+ T cells reflected nephritis activity, and elevation above 800 CD4+ T cells per 100 ml of urine sharply delineated active from inactive nephritis. CONCLUSION: CXCR3+ T cells are recruited into the inflamed kidneys, are enriched in the urine, and are a valuable marker of nephritis activity in SLE. They also present a potential target for future therapies.

Psicosis



1: Rheumatology (Oxford). 2008 Oct;47(10):1498-502.

Psychosis due to systemic lupus erythematosus: characteristics and long-term outcome of this rare manifestation of the disease.

Pego-Reigosa JM, Isenberg DA.

Centre for Rheumatology Research, University College of London Division of Medicine, London, UK. jose.maria.pego.reigosa@sergas.es

OBJECTIVE: To determine the prevalence, characteristics and long-term outcome of psychosis due to SLE defined according to the ACR nomenclature for neuropsychiatric (NP) syndromes. METHODS: All the patients who strictly fulfilled the ACR definition for psychosis due to lupus were identified within the 485 patients of our lupus cohort and retrospectively evaluated. RESULTS: Psychosis due to lupus was diagnosed in 11 (2.3%) patients. Lupus psychosis presented as the initial presentation of SLE in 60% of the patients and within the first year of the disease in 80% of the cases. All the patients developed psychotic symptoms within the context of multi-systemic lupus activity, with 90% of them having cutaneous involvement. Psychosis activity in our patients was associated with biological markers of lupus activity in 90% of the cases. The aPLS were observed in 10% of the cases. Seventy percent of our patients showed complete resolution of psychotic symptoms after a mean follow-up of 155 months. Long-lasting remissions were seen in all those patients. Chronic mild psychotic symptoms were observed in 30% of our patients. CONCLUSION: Psychosis due to lupus is an uncommon event that usually occurs early in the course of the disease and is associated with other clinical and biological features of SLE. Long-term outcome appears to be favourable after intensive immunosuppressive treatment. This report highlights the need for prospective multi-centre studies to improve our knowledge and to help establish guidelines for the treatment of this rare complication of lupus.

Discapacidad

1: Arthritis Rheum. 2008 Oct 15;59(10):1475-9.

Employment and disability issues in systemic lupus erythematosus: a review.

Scofield L, Reinlib L, Alarcón GS, Cooper GS.

National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA.

OBJECTIVE: To summarize research pertaining to work disability in lupus patients, discuss challenges patients face applying for federal disability assistance in the US, and make recommendations for clinical and health policy research. METHODS: We searched Medline for articles on work or disability in lupus patients and gathered information from the Social Security Administration and the National Organization of Social Security Claimants' Representatives. RESULTS: We found 12 publications with employment-related data; 6 included analysis of predictors of work status. The prevalence of inability to work or cessation of work was 15-51% in these studies (3-15 years after diagnosis); 20-32% of patients received disability benefits. Lower education level, higher disease activity, higher disease damage, older age, and higher physical job strain were independent predictors of work disability or work cessation in at least 2 studies. Lupus patients may be less successful than patients with other diseases when applying for federal disability assistance, possibly because medical records may not accurately reflect functional limitations. In addition, symptoms contributing to work disability (e.g., fatigue, pain, neurocognitive dysfunction) may be difficult to assess and quantify. CONCLUSION: Work disability in lupus patients is common. Additional research on risk factors for work disability in lupus patients and on strategies for reducing the impact of these factors on work-related activities is needed. The development of better measures and rating scales for the symptoms responsible for work disability in lupus patients and studies of factors influencing the success of obtaining federal disability benefits would also be useful.

PMID: 18821684 [PubMed - indexed for MEDLINE]

1: Arthritis Rheum. 2008 Jul 15;59(7):984-8.

Functional outcome after stroke in patients with rheumatoid arthritis and systemic lupus erythematosus.

Nguyen-Oghalai TU, Wu H, McNearney TA, Granger CV, Ottenbacher KJ.

Division of Rheumatology, University of Texas Medical Branch, Galveston, TX 77555, USA. tranguye@utmb.edu

OBJECTIVE: To compare outcomes following stroke rehabilitation among patients with rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) versus patients with neither RA nor SLE (non-RA/SLE). METHODS: We conducted a retrospective analysis using a national database of patients with stroke admitted to inpatient rehabilitation between 1994 and 2001. Primary outcomes were discharge disposition and functional status, rated by the Functional Independence Measure (FIM) Instrument, at discharge and at followup. The independent variable was RA or SLE. Covariates were age, sex, race/ethnicity, admission FIM ratings, additional comorbidities (none, 1-3, and >3), type of stroke, and length of stay. RESULTS: We studied 47,853 patients with stroke, 368 with RA, and 119 with SLE. Discharge dispositions were similar for patients with RA and non-RA/SLE (81% discharged home). At discharge, the average FIM rating for patients with RA was 85.8, compared with 87.8 for non-RA/SLE patients. At followup, the average FIM rating for patients with RA was 95.9, compared with 99.6 for non-RA/SLE patients. RA was associated with lower FIM ratings at discharge and followup in multivariate analyses. SLE was associated with younger age (17.5 years). However, patients with SLE had similar discharge dispositions and FIM ratings to non-RA/SLE patients. CONCLUSION: RA was associated with lower functional status ratings at discharge and followup. Outpatient therapy for patients with RA may reduce long-term assistance. Patients with SLE were younger, but had similar functional outcomes to patients without RA/SLE, suggesting early morbidity from stroke among patients with SLE.

LES varón

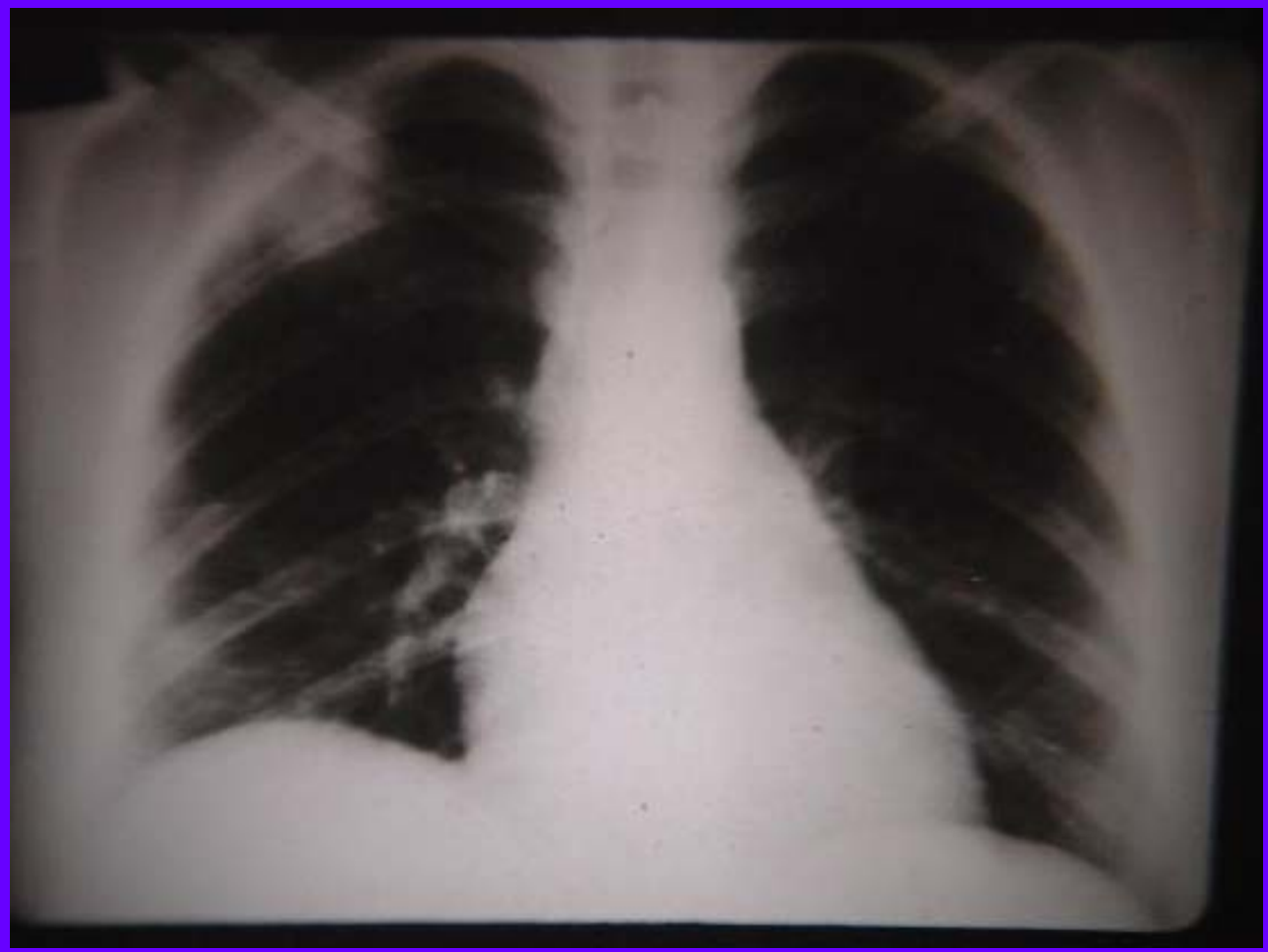
1: Rheumatology (Oxford). 2008 Nov;47(11):1692-7. Epub 2008 Sep 11.

Testicular Sertoli cell function in male systemic lupus erythematosus.

Suehiro RM, Borba EF, Bonfa E, Okay TS, Cocuzza M, Soares PM, Silva CA.

Division of Rheumatology, Department of Pediatrics, University of São Paulo, SP, Brazil.

OBJECTIVE: To assess the testicular Sertoli cell function in male SLE patients. METHODS: Thirty-four consecutive patients were prospectively selected to evaluate serum inhibin B. Clinical features, treatment, semen analysis, urological evaluation, testicular ultrasound, hormones and anti-sperm antibodies were determined. RESULTS: Patients were subdivided into two groups: low serum inhibin B (Group 1, n = 8) and normal levels (Group 2, n = 26). The median sperm concentration (P = 0.024), total sperm count (P = 0.023) and total motile sperm count (P = 0.025) were lower in Group 1. Inhibin B levels were positively correlated with sperm concentration (r = 0.343), total motile sperm count (r = 0.357), and negatively correlated with follicule-stimulating hormone (FSH) (r = 0.699) and luteinizing hormone (r = 0.397). The median serum inhibin B was lower in SLE patients treated with intravenous cyclophosphamide (IVCYC) compared with those without this therapy (P = 0.031). Further evaluation of the 26 SLE patients with normal inhibin B and FSH levels revealed that medians of inhibin B/FSH ratio were lower in SLE patients with oligozoospermia compared with normozoospermia (P = 0.004). This ratio was also lower in SLE patients treated with IVCYC than those without this therapy (P = 0.04). In contrast, inhibin B serum level alone did not discriminate the later group of patients (P = 0.12). CONCLUSIONS: This is the first study to identify a high frequency of testicular Sertoli cell dysfunction in male SLE associated with semen abnormalities. Further prospective studies are necessary to determine if inhibin levels and inhibin B/FSH ratio will be an earlier and useful marker of IVCYC toxicity in these patients.



Infecciones

- **Medicine (Baltimore). 2008 Nov;87(6):311-8. Acute viral infections in patients with systemic lupus erythematosus: description of 23 cases and review of the literature.** Ramos-Casals M, Cuadrado MJ, Alba P, Sanna G, Brito-Zerón P, Bertolaccini L, Babini A, Moreno A, D'Cruz D, Khamashta MA.
  - Cases occurring within the last 5 years. MEDLINE 1985 - 2008.
  - 88 cases (23 from our clinics and 65 from the literature review)
  - 25 patients were diagnosed with new-onset SLE (fulfillment of the 1997 SLE criteria) associated with infection by human parvovirus B19 (n = 15), cytomegalovirus (CMV; n = 6), Epstein-Barr virus (EBV; n = 3), and hepatitis A virus (n = 1).
  - The remaining 63 cases of acute viral infections arose in patients already diagnosed with SLE: in 18 patients, symptoms related to infection mimicked a lupus flare, 36 patients, including 1 patient from the former group who presented with both conditions, presented organ-specific viral infections (mainly pneumonitis, colitis, retinitis, and hepatitis), and 10 patients presented a severe, multiorgan process similar to that described in catastrophic antiphospholipid syndrome-the final diagnosis was hemophagocytic syndrome in 5 cases and disseminated viral infection in 5.

- Twelve patients died due to infection caused by CMV (n = 5), herpes simplex virus (n = 4), EBV (n = 2), and varicella zoster virus (n = 1).
- The most common viral infections in patients with SLE are parvovirus B19 (predominantly mimicking SLE presentation) and CMV (predominantly presenting in severely immunosuppressed patients).
- CMV infection may mimic a lupus flare or present with specific organ involvement such as gastrointestinal bleeding or pulmonary infiltrates. Other herpesviruses are common in immunosuppressed SLE patients and may produce a wide range of manifestations.
- Physicians should examine the pharynx, eyes, skin, and genitalia and should conduct serologic and molecular studies to improve early detection of viral infection in patients with SLE.

1: Rheumatology (Oxford). 2008 Sep;47(9):1352-7. Epub 2008 Jun 19.

Long-term outcome and short-term survival of patients with systemic lupus erythematosus after bacteraemia episodes: 6-yr follow-up.

Chen MJ, Tseng HM, Huang YL, Hsu WN, Yeh KW, Wu TL, See LC, Huang JL.

Division of Allergy, Asthma and Rheumatology, Department of Pediatrics, Chang Gung Children's Hospital, Taoyuan, Taiwan 5, Fu-Hsin Street, Kweishan, Taoyuan, Taiwan.

OBJECTIVE: To describe the nature of bacteraemia in SLE patients and determine the short-term survival and long-term outcome of these patients. METHODS: Analysis of the medical records of 1442 SLE patients who were regularly followed up in a tertiary teaching medical centre from 2000 to 2005. RESULTS: Among 1442 SLE patients, 240 patients (17%) developed at least one episode of bacteraemia, corresponding to an incidence of 92.7 cases/1000 hospital admissions. Since SLE diagnosis, the overall survival of our patients was 92% at 5 yrs, 86% at 10 yrs and 79% at 15 yrs. However, after one episode of bacteraemia, the survival decreased to 76% at 30 days and 67% at 360 days. Of the 336 episodes of bacteraemia, 167 were community-acquired (49.7%) and 169 were nosocomial (50.3%). Staphylococcus aureus was the leading cause of Gram-positive bacteraemia. Among Gram-negative bacteria, non-typhoidal Salmonella and Escherichia coli were the most common species. Community-acquired Salmonella and Streptococcus bacteraemia were more common than nosocomial infections. Klebsiella and Acinetobacter spp. were significantly more responsible for nosocomial than community-acquired bacteraemia. Patients infected with Acinetobacter, Klebsiella or Pseudomonas had lower probabilities of 14-day survival (71.4, 55.6, 42.9%, respectively). CONCLUSIONS: Among SLE patients, an episode of bacteraemia was associated with an unfavourable long-term outcome. The bacterial species significantly influenced short-term survival. Therefore, when empiric antibiotic therapy is initiated in SLE patients who are suspected of bacteraemia, we suggest use of antibiotics that are effective against Pseudomonas, Klebsiella, Acinetobacter, S. aureus, and E. coli.

Aterosclerosis

1: Rheumatology (Oxford). 2009 Jan;48(1):26-31. Epub 2008 Nov 10.

Anti-atherogenic and anti-inflammatory properties of high-density lipoprotein are affected by specific antibodies in systemic lupus erythematosus.

Batuca JR, Ames PR, Amaral M, Favas C, Isenberg DA, Delgado Alves J.

Pharmacology Department, Faculty of Medical Sciences of Lisbon, Lisbon, Portugal.

OBJECTIVE: To determine whether antibodies against high-density lipoprotein (aHDL) and apolipoprotein A-I (aApo A-I) interfere with the anti-atherogenic functions of high-density lipoprotein (HDL) and relate to disease activity and damage in SLE. METHODS: Seventy-seven SLE patients were compared with an age- and sex-frequency matched control group. Immunoglobulin G (IgG) aHDL, IgG aApoA-I, soluble vascular cell and intracellular cell adhesion molecules (VCAM-1 and ICAM-1, respectively) were measured by ELISA, paraoxonase (PON) activity by spectrophotometry, nitric oxide (NOx) metabolites by the Griess reaction, and total anti-oxidant capacity (TAC) by chemiluminescence. RESULTS: Compared with controls, SLE patients showed higher titres of IgG aHDL ($P < 0.0001$) and IgG aApo A-I ($P < 0.0001$), lower PON activity ($P < 0.0001$), increased NOx ($P < 0.0001$), VCAM-1 ($P < 0.0001$) and ICAM-1 ($P = 0.0008$) and lower TAC ($P = 0.0006$). Titres of IgG aHDL positively correlated with IgG aApo A-I ($r = 0.64$, $P < 0.0001$), NOx ($r = 0.32$, $P = 0.007$), inversely correlated with PON activity ($r = -0.34$, $P = 0.002$) and TAC ($r = -0.43$, $P = 0.0004$) and were independently associated with ICAM-1 ($t = 3.509$, $P = 0.001$). IgG aApo A-I titres correlated positively with NO ($r = 0.37$, $P = 0.007$), inversely with PON activity ($r = -0.31$, $P = 0.006$), TAC ($r = -0.47$, $P < 0.0001$) and were independently associated with HDL ($t = -2.747$, $P = 0.008$) and VCAM-1 ($t = 3.311$, $P = 0.002$), the latter alongside NOx ($T = 2.271$, $P = 0.02$). Elevated titres of IgG aHDL and IgG aApo A-I and reduced PON activity related to increased disease score (BILAG) and damage index (SLICC/ACR DI). CONCLUSION: In SLE, IgG aHDL and aApo A-I associate with disease activity and damage and interfere with the anti-oxidant and anti-inflammatory functions of HDL favouring atherogenesis.

1: Am J Med. 2008 Oct;121(10 Suppl 1):S3-8.

Subclinical atherosclerosis in rheumatoid arthritis and systemic lupus erythematosus.

Salmon JE, Roman MJ.

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Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are associated with increased mortality, largely as a consequence of cardiovascular disease. Increased cardiovascular morbidity and mortality in patients with RA and SLE cannot be entirely explained by traditional risk factors, suggesting that the systemic inflammation that characterizes these diseases may accelerate atherosclerosis. We used carotid ultrasonography to investigate the prevalence and correlates to preclinical atherosclerosis in patients with RA and SLE. Because atherosclerosis is a systemic disease, assessment of carotid plaque by ultrasonography provides a robust, direct measure of systemic atherosclerosis. We observed a substantially increased prevalence of carotid plaque in RA and SLE patients compared with age- and sex-matched controls, which remained after adjustment for traditional risk factors. The presence of carotid atherosclerosis was associated with disease duration in both RA and SLE and damage in SLE. These data support the hypothesis that inflammation associated with RA and SLE contributes to accelerated atherosclerosis and argue that RA and SLE disease activity should be more aggressively managed.

1: Am J Cardiol. 2008 Sep 15;102(6):755-60. Epub 2008 Jun 26.

C-reactive protein and coronary artery calcium in asymptomatic women with systemic lupus erythematosus or rheumatoid arthritis.

Kao AH, Wasko MC, Krishnaswami S, Wagner J, Edmundowicz D, Shaw P, Cunningham AL, Danchenko N, Sutton-Tyrrell K, Tracy RP, Kuller LH, Manzi S.

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Patients with systemic lupus erythematosus (SLE) and those with rheumatoid arthritis (RA) have increased risk for atherosclerotic cardiovascular disease. The aims of this study were to compare the presence of coronary artery calcium (CAC) in age- and race-matched women with SLE, those with RA, and healthy controls without diabetes mellitus or history of myocardial infarction, angina pectoris, or stroke and to investigate its relation with traditional risk factors, inflammation, and endothelial activation. Study subjects completed cardiovascular risk factor assessment and electron-beam computed tomography that measured CAC. The 2 patient groups had similar prevalence and extent of CAC as well as significantly increased odds of having any CAC (odds ratio 1.87, 95% confidence interval 1.09 to 3.21) and more extensive CAC (odds ratio 4.04, 95% confidence interval 1.42 to 11.56 for CAC score >100) compared with healthy controls. After controlling for differences in cardiovascular risk factors, including insulin resistance and hypertension, the results remained statistically significant. After adjustment for differences in levels of C-reactive protein and/or soluble intercellular adhesion molecule-1, however, women with chronic inflammatory diseases no longer had significantly increased odds of having any CAC or more extensive CAC compared with controls. In conclusion, asymptomatic and nondiabetic women with chronic inflammatory diseases had significantly increased odds of having CAC and more extensive CAC compared with age- and race-matched healthy controls. The increased odds for CAC may in part result from higher levels of inflammation and endothelial activation in these patients.

1: Rheumatology (Oxford). 2008 Oct;47(10):1476-83. Epub 2008 Jul 26.

Comment in:
Rheumatology (Oxford). 2009 Apr;48(4):453; author reply 453-4.

Systemic lupus erythematosus patients exhibit functional deficiencies of endothelial progenitor cells.

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OBJECTIVE: SLE is characterized by an increased cardiovascular risk. Since endothelial progenitor cells (EPCs) have been described to serve as a biomarker for the CV risk and are known to be depleted in various diseases, we were interested if SLE would also be associated with altered peripheral EPC levels or functional abnormalities of these cells. METHODS: EPCs were quantified in 31 female SLE patients with different disease activity and in age-matched healthy controls (HCs) by FACS analysis and by colony forming unit (CFU) assay. Furthermore, EPC adhesion and migration capacity were tested. RESULTS: EPC levels were similar in HC and SLE when assessed by FACS (0.045 +/- 0.006% vs 0.036 +/- 0.007% within the lymphocyte gate) and by the CFU assay (18 +/- 3 vs 15 +/- 2 colonies/well). No correlation with disease activity could be observed, but SLE patients treated with chloroquine exhibited significantly decreased EPC levels (0.058 +/- 0.005% without vs 0.024 +/- 0.008% with chloroquine, $P < 0.05$). Addition of chloroquine to in vitro cultures also led to a decreased colony formation in SLE and in HC. When testing the adhesion and migration capacity of EPC on human umbilical vein endothelial cells (HUVEC), cells from SLE patients had reduced adhesion (19.2 +/- 3.5% vs 36.6 +/- 5.2% EPC/high power field, $P < 0.02$) and migratory activity (56 +/- 6 cells/random microscopic field in SLE vs 121 +/- 28 in controls, $P < 0.02$). CONCLUSION: The data reveal that EPCs are significantly affected in SLE. While circulating EPC levels are in the range of HC, they exhibit functional deficiencies that may lead to impaired tissue availability.

1: Transl Res. 2009 Feb;153(2):51-9. Epub 2008 Dec 9.

Differences in subclinical cardiovascular disease between African American and Caucasian women with systemic lupus erythematosus.

Rhew EY, Manzi SM, Dyer AR, Kao AH, Danchenko N, Barinas-Mitchell E, Sutton-Tyrrell K, McPherson DD, Pearce W, Edmundowicz D, Kondos GT, Ramsey-Goldman R.

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Racial differences exist in disease rates and mortality in both cardiovascular disease (CVD) and systemic lupus erythematosus (SLE). The objective of this cross-sectional study was to compare the frequency and risk factors for subclinical CVD in African American (AA) and Caucasian women with SLE and no prior CVD events. Traditional CVD risk factors and SLE-related factors were assessed in 309 SLE women. Subclinical CVD was assessed by carotid ultrasound to measure intimamedial thickness (IMT) and plaque, and electron beam computed tomography (EBCT) was used to measure coronary artery calcium (CAC). AA women had less education and higher levels of body mass index, blood pressure, lipoprotein(a), C-reactive protein (CRP), fibrinogen, and erythrocyte sedimentation rate (ESR). However, AA women had lower albumin, more and longer duration of corticosteroid use, higher SLE disease activity and damage, and more dsDNA antibodies compared with Caucasian women after adjustment for age and study site. More AA women had carotid plaque (adjusted odds ratio [OR], 1.94; 95% confidence interval [CI], 1.03-3.65) and higher carotid IMT (0.620 vs 0.605 mm, P = 0.07) but similar CAC compared with Caucasians. A multivariate analysis revealed that the following risk factor variables were significantly different between the racial groups and associated with plaque: blood pressure, current corticosteroid use, SLE disease activity, and SLE damage. All factors contributed to the result, but no individual risk factor fully accounted for the association between race and plaque. In conclusion, the presence of carotid plaque was higher in AA compared with Caucasian women with SLE, in contrast to studies of non-SLE subjects, in which AA have similar or less plaque than Caucasians. A combination of SLE-related and traditional CVD risk factors explained the racial difference in plaque burden.

1: Lupus. 2009;18(6):479-85.

Lupus and cancer.

Gayed M, Bernatsky S, Ramsey-Goldman R, Clarke A, Gordon C.

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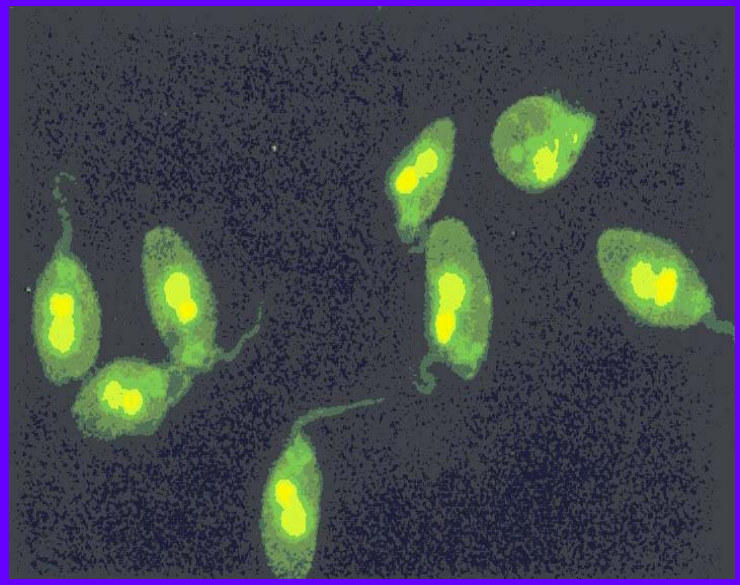
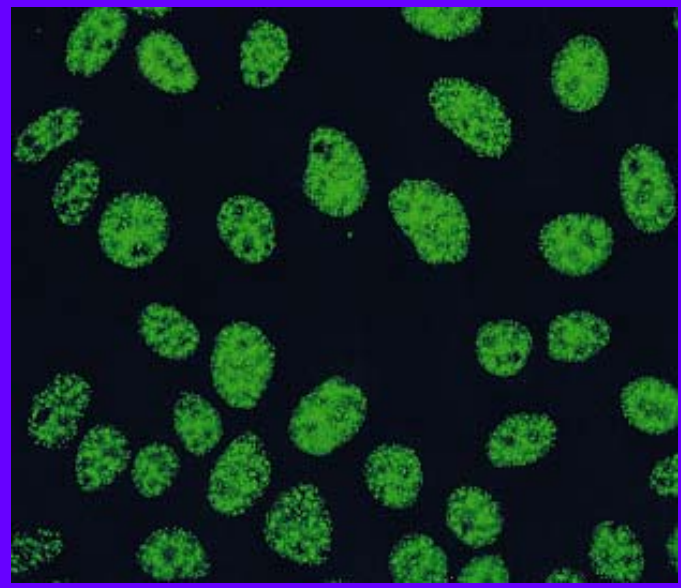
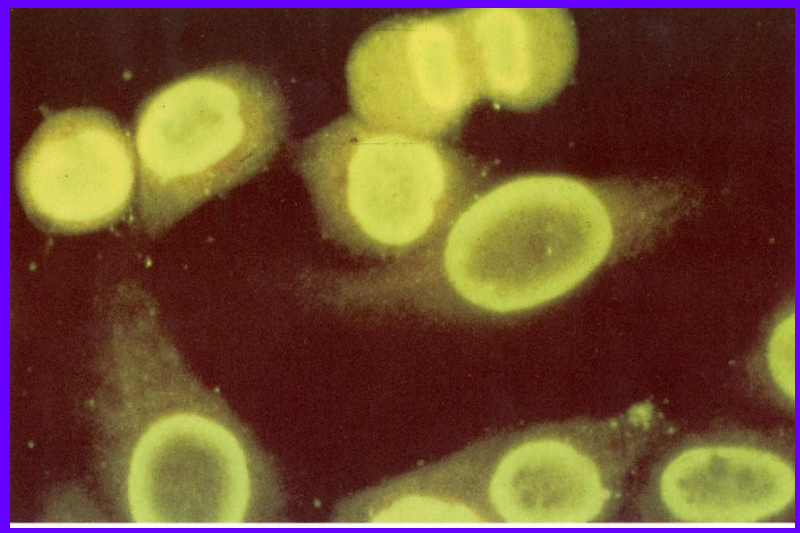
Individuals with systemic lupus erythematosus (SLE) have an increased susceptibility to certain types of cancer. Of particular concern are haematologic malignancies, specifically non-Hodgkin lymphoma, where a three- to four-fold increased risk is seen in SLE, compared with the general population. There is some evidence that immunosuppressive exposures play a role, although there appear to be other factors driving the risk. Lupus disease activity, with resultant dysregulated lymphocyte proliferation, may itself be a mediator of the association between SLE and lymphoma. Aside from haematologic malignancy risk, lung cancer also is increased in SLE compared with the general population, and smoking likely drives this risk in large part. Last but not least, cervical dysplasia is a concern in women with SLE, particularly with exposure to immunosuppressants; routine screening for this complication should not be neglected.







Concentration of antibodies to extractable nuclear antigens and disease activity in systemic lupus erythematosus.

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A hallmark of systemic lupus erythematosus (SLE) is the production of autoantibodies directed against intracellular antigens. Antibodies to double stranded DNA (dsDNA) are most closely associated with the clinical manifestations of the condition and appear to have a direct role in pathogenesis. On the contrary, the relationship between disease activity in SLE and anti-extractable nuclear antigen (ENA) antibodies has not been well demonstrated. Despite this, commercial assays for the quantification of anti-ENA antibodies are now widely available, although their usefulness in clinical practice is not known. The aim of this study was to investigate whether there is an association between disease activity in SLE and concentrations of individual anti-ENA antibodies. A prospective 2-year study of 45 patients with SLE, known to be positive for at least one anti-ENA antibody, was performed. Disease activity was assessed using the SLE Disease Activity Index (SLEDAI). Anti-ENA antibodies were quantified using a commercial antibody detection system. A total of 45 patients were studied over a 2-year period (median number of assessments 5, range 2-9). Of them 29 patients were positive for Ro, 8 for La, 9 for Sm and 27 for RNP antibodies. In the population as a whole, there was a weak relationship between peak SLEDAI score and anti-Sm concentration ($r = 0.57$, NS), but no relation with the other anti-ENA antibodies. In a small number of patients, there appeared to be either a positive (Ro, Sm) or negative (La, Sm, RNP) association between ENA antibody concentration and disease activity over time; however, this was not apparent for the majority of individuals. These results show that in SLE, clinically significant changes in disease activity do not correlate well with concentrations of anti-ENA antibodies, either within the population as a whole or on an individual basis. Repeated quantitative measurement of anti-ENA antibodies does not therefore appear to provide useful additional information in assessing disease activity in SLE. The widespread application of commercial quantitative assays to routine clinical practice is not recommended.

1: Lupus. 2009 Mar;18(3):223-9.

Anti-nucleosome and anti-chromatin antibodies are present in active systemic lupus erythematosus but not in the cutaneous form of the disease.

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The objective of this study is to investigate the presence of anti-nucleosome (anti-NCS) and anti-chromatin (anti-CRT) antibodies in patients with cutaneous lupus erythematosus (CLE) compared with active and inactive systemic lupus erythematosus (SLE). A total of 154 subjects were evaluated: 54 patients presenting CLE, 66 patients with active SLE and 34 with inactive SLE. Lupus activity was assessed using the disease activity index (SLEDAI). Anti-NCS and anti-CRT antibodies were detected by enzyme-linked immunosorbent assay (ELISA). Only one of 54 patients with CLE tested positive for both anti-NCS and anti-CRT antibodies. The prevalence of anti-CRT antibodies was significantly higher in active SLE (84.8%) when compared with inactive SLE (26.4%) and CLE (1.8%) ($P < 0.001$). Anti-NCS antibodies were also more prevalent in active SLE patients (74.2%) than inactive SLE (11.7%) and CLE patients (1.8%) ($P < 0.001$). The presence of anti-CRT and anti-NCS antibodies was correlated to disease activity in patients with SLE ($r = 0.4937$, $r = 0.5621$, respectively). Furthermore, the detection of both antibodies was correlated with disease activity in patients with SLE who tested negative for anti-dsDNA antibodies ($r = 0.4754$ for anti-NCS and $r = 0.4281$ for anti-CRT). The presence of these two auto-antibodies was strongly associated with renal damage in patients with SLE (OR = 13.1, for anti-CRT antibodies and OR = 25.83, for anti-NCS antibodies). The anti-NCS and anti-CRT antibodies were not found in CLE. In patients with SLE, there is a correlation of these antibodies with disease activity and active nephritis. When compared with anti-dsDNA antibodies, anti-NCS and anti-CRT antibodies were more sensitive in detecting disease activity and kidney damage in lupus patients.

1: Lupus. 2009;18(6):539-46.

Autoantibodies against galectin-8: their specificity, association with lymphopenia in systemic lupus erythematosus and detection in rheumatoid arthritis and acute inflammation.

Massardo L, Metz C, Pardo E, Mezzano V, Babul M, Jarpa E, Guzmán A, André S, Kaltner H, Gabius H, Jacobelli S, González A, Soza A.

Departamento de Inmunología Clínica y Reumatología, Pontificia Universidad Católica de Chile, Santiago, Chile.

The role of autoantibodies in the pathogenesis of systemic lupus erythematosus (SLE) has not been completely defined. From more than a hundred autoantibodies described in SLE, relatively few have been associated with clinical manifestations. The glycan-binding proteins of the galectin family can modulate the immune system. Anti-galectin autoantibodies thus could have functional and/or pathogenic implications in inflammatory processes and autoimmunity. We previously reported function-blocking autoantibodies against galectin-8 (Gal-8) in SLE. Here we tested these autoantibodies against a series of other human galectins and demonstrated their specificity for Gal-8, being detectable in 23% of 78 SLE patients. Remarkably, they associated with lymphopenia (50% of 18 anti-Gal-8-positive versus 18% of 60 anti-Gal-8-negative cases, Fisher's Exact test two-tailed: $P < 0.012$). Lymphopenia is a common clinical manifestation in SLE, yet of unknown mechanism. In addition, six of eight patients with both lymphopenia and malar rash had anti-Gal-8 in their sera. Occurrence of these autoantibodies was not confined to SLE as we also found them in sera of patients with rheumatoid arthritis (16%) and septicemia (20%). This study thus establishes occurrence of specific anti-Gal-8 autoantibodies in autoimmune rheumatic diseases and in acute inflammation, with an apparent association to a clinical subset in SLE.

Tratamiento

genoxal

Primer citostático de acción selectiva sobre el órgano enfermo sin apenas afectar órganos hematopoyéticos normales, para el tratamiento de tumores malignos, rereticulosis, hematodermias, etc.

Su uso en el pre y post-operatorio es de gran utilidad para evitar las diseminaciones y recidivas.

composición

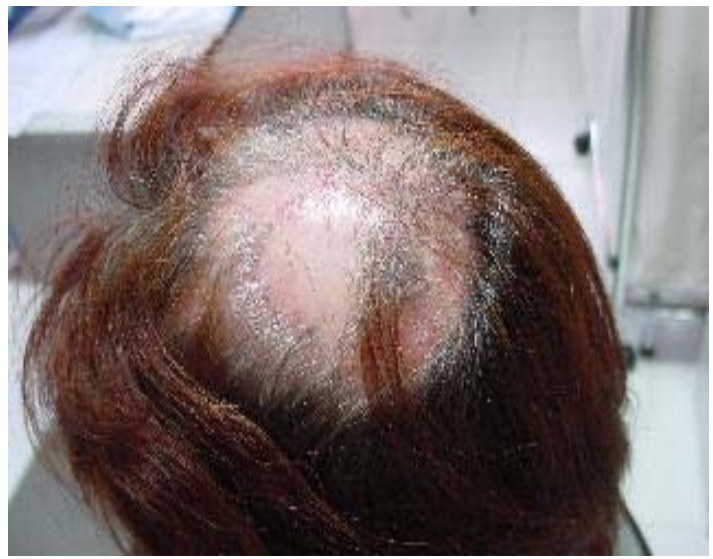
Por ampolla: 200 mg. de GENOXAL (éster N. N. bis [β-cloroetil]-N'-O-propilénico de la diamida del ácido fosfórico) y 45 mg. de cloruro sódico para mezclar con 10 c. c. de agua destilada en el momento de su uso.

Por gragea: 50 mg. de GENOXAL (éster N. N. bis [β-cloroetil]-N'-O-propilénico de la diamida del ácido fosfórico).

INCLUIDO EN EL S. O. E. Libre prescripción

LABORATORIOS FUNK, S. A. · MALLORCA, 288 · BARCELONA · 9

- **Shah A**, Arch Dermatol. 2009 Mar;145(3):316-9.
  - **Lenalidomide for the treatment of resistant discoid lupus erythematosus.**



1: Arthritis Rheum. 2008 Dec 15;59(12):1796-804.

Steroid-sparing effects of methotrexate in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial.

Fortin PR, Abrahamowicz M, Ferland D, Lacaille D, Smith CD, Zummer M; Canadian Network For Improved Outcomes in Systemic Lupus.

Collaborators (26)

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OBJECTIVE: To assess the potential benefits of methotrexate in patients with systemic lupus erythematosus (SLE). METHODS: A 12-month, double-blind, placebo-controlled trial of methotrexate with folic acid was conducted. Intent-to-treat analyses were performed with mixed linear models and alpha = 0.04 (96% confidence interval [96% CI]) to account for interim analysis of longitudinal data to assess the treatment effects on lupus disease activity and daily steroid dose across monthly measurements, and to test if the treatment effects depended on selected participant characteristics. RESULTS: Of 215 participants screened, 94 were excluded, 35 declined, and 86 were randomized (methotrexate = 41, placebo = 45). The groups were balanced for demographic and disease characteristics. Antimalarial use was more frequent in the placebo group, which was adjusted for in multivariable analyses. Sixty participants (27 methotrexate, 33 placebo) completed the study and 26 terminated early. Among participants who had the same baseline prednisone dose, those taking methotrexate received, on average, 1.33 mg/day less prednisone during the trial period (96% CI 0.06, 2.72 mg/day; a 22% reduction of their average-during-trial daily dose) compared with those in the placebo group. For the primary measure of disease activity (revised Systemic Lupus Activity Measure), methotrexate use was also associated with a marginally significant reduction in the mean during-trial score of 0.86 units (96% CI 0.01, 1.71; P = 0.039). A significant interaction between treatment and baseline damage was found (P = 0.001). CONCLUSION: Methotrexate conferred a significant advantage in participants with moderately active lupus by lowering daily prednisone dose and slightly decreasing lupus disease activity. As a therapeutic option in moderate SLE, methotrexate can be considered to be steroid sparing.

1: Lupus. 2009 Feb;18(2):139-43.

Mycophenolate mofetil for the treatment of juvenile onset SLE: a multicenter study.

Falcini F, Capannini S, Martini G, La Torre F, Vitale A, Mangiantini F, Nacci F, Cerinic MM, Cimaz R, Zulian F.

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Mycophenolate mofetil (MMF) has proved to be an efficacious and safe therapy in adult lupus nephritis. Recently, this drug has been suggested as a possible new alternative treatment also for juvenile-onset SLE (juvenile-SLE). A multicenter study has been performed to evaluate the efficacy and safety of MMF in controlling the disease activity in children and adolescents with juvenile-SLE. Our results show that MMF was effective in reducing the disease activity or as a steroid-sparing agent in 14 of 26 patients (54%), stabilised the disease in 8 (31%) and was ineffective in 4 (15%). In particular, in patients without renal involvement, a good response was registered in 9 of 13 patients (69%). Among those patients with renal involvement, MMF was effective in 5 of 13 patients (38%), partially effective in 4 (31%) and ineffective in 4 (31%). No severe side effects have been observed; only two patients stopped the drug because of severe diarrhoea and abdominal pain. With the limits of a retrospective study, MMF seems to be effective and safe for the treatment of juvenile-SLE, especially in patients with no renal involvement.

1: Clin Pharmacol Ther. 2009 May;85(5):527-30. Epub 2009 Jan 7.

Pro32Thr polymorphism of inosine triphosphate pyrophosphatase gene predicts efficacy of low-dose azathioprine for patients with systemic lupus erythematosus.

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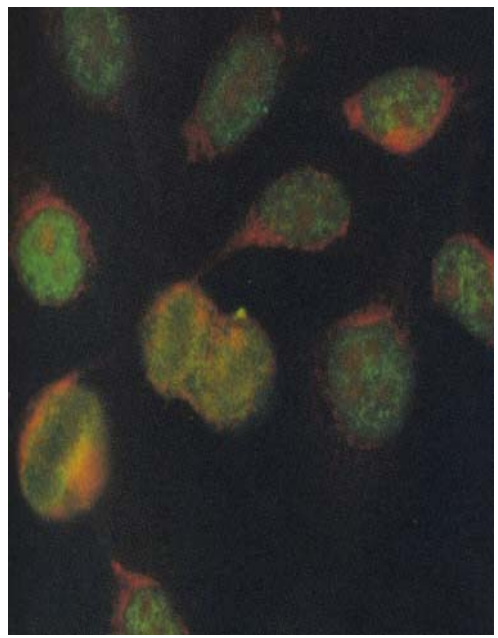
We evaluated the relationship between the efficacy of low-dose azathioprine (AZA) therapy and the inosine triphosphate pyrophosphatase (ITPA) 94C>A (Pro32Thr) polymorphism in patients with systemic lupus erythematosus (SLE). We performed a multiple regression analysis to assess the influence of various factors on the reduction in SLE disease activity index (SLEDAI) scores. The ITPA 94C>A polymorphism had the highest correlation with the change in SLEDAI score ($r = 0.354$, $P = 0.006$).

Rein AJ, et Jerusalem, Israel .
Early diagnosis and treatment of atrioventricular block in the fetus exposed to maternal anti-SSA/Ro-SSB/La antibodies: a prospective, observational, fetal kinetocardiogram-based study.
Circulation. 2009;119:1867-72.

- **FKCG in 70 fetuses of 56 mothers who were + for anti-SSA/Ro and/or SSB/La.**
- **CONCLUSIONS:**
  - **FKCG can detect first-degree AVB in the fetus exposed to maternal anti-SSA/Ro or anti-SSB/La antibodies (or both).**
  - **Dexamethasone given on detection was associated with normalized AV conduction in fetuses with first-degree AVB.**
  - **No fetus in the present study developed complete prenatal or postnatal AVB.**



1: Arthritis Rheum. 2009 Feb 15;61(2):240-6.

Depression, medication adherence, and service utilization in systemic lupus erythematosus.

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OBJECTIVE: Forgetting to take medications is an important cause of nonadherence. This study evaluated factors associated with forgetting to take medications in a large cohort of persons with systemic lupus erythematosus (SLE) participating in the University of California, San Francisco Lupus Outcomes Study (LOS). Relationships among adherence problems and service utilization (outpatient visits, emergency department visits, and hospitalizations) were also evaluated. METHODS: The cohort consisted of 834 LOS participants who provided self-reported frequency of forgetting to take medications as directed. Predictors of adherence and service utilization patterns included self-reported sociodemographics, disease-related characteristics (e.g., disease activity, recent SLE flare), and mental health characteristics (Center for Epidemiologic Studies Depression Scale and cognitive function screen). Health care utilization patterns included the presence and quantity of visits to rheumatologists, primary care physicians, other care providers, emergency departments, and hospitalizations. RESULTS: Forty-six percent of the LOS cohort reported forgetting to take medications at least some of the time. Depressive symptom severity was a strong predictor of adherence difficulties (odds ratio [OR] 1.04, 95% confidence interval [95% CI] 1.02-1.05; $P < 0.0001$) after accounting for all other predictors. Persons reporting adherence difficulties had significantly greater numbers of outpatient rheumatology and primary care visits, and were more likely to visit the emergency department (OR 1.45, 95% CI 1.04-2.04; $P = 0.03$). CONCLUSION: Depression may be an important cause of medication adherence problems, and difficulties with adherence are significantly associated with high-cost service utilization, specifically emergency department visits. In an era of rapidly evolving treatments for lupus, identifying patients at risk for adherence problems may decrease medical expenditures and improve patient outcomes in SLE.

1: Rheumatology (Oxford). 2008 Oct;47(10):1506-9. Epub 2008 Jul 26.

Fertility preservation treatment for young women with autoimmune diseases facing treatment with gonadotoxic agents.

Elizur SE, Chian RC, Pineau CA, Son WY, Holzer HE, Huang JY, Gidoni Y, Levin D, Demirtas E, Tan SL.

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shai.elizur@gmail.com

OBJECTIVE: To describe a case series of seven women with SLE and other systemic autoimmune rheumatic diseases (SARDs) who required cyclophosphamide therapy and underwent fertility preservation treatments. METHODS: Of the seven patients reported here, five women had SLE with nephritis, the sixth had immune thrombocytopenia purpura (ITP) and the seventh had microscopic polyangiitis (MPA) with renal involvement. All women were nulliparous and younger than 35 yrs. RESULTS: Patients with SLE underwent in vitro maturation (IVM) of immature oocytes aspirated during a natural menstrual cycle followed by vitrification of the matured oocytes if a male partner was not available, or vitrification of embryos if one was available. The patient with ITP and the patient with MPA underwent gonadotropin ovarian stimulation followed by oocyte or embryo vitrification. All women completed fertility preservation treatment successfully and mature oocytes or embryos (36 and 13, respectively) were vitrified. No complications were associated with this treatment and cytotoxic therapy was initiated as scheduled in all cases. CONCLUSIONS: Oocyte or embryo cryopreservation should be considered for fertility preservation in young women with SARDs who face imminent gonadotoxic treatment. In patients, where gonadotropin ovarian stimulation is deemed unsafe, IVM of immature oocytes, aspirated during a natural menstrual cycle, followed by vitrification or fertilization of the mature oocytes, seems to be safe and feasible. For patients in whom hormonal ovarian stimulation is not contraindicated, this method may be considered depending on the urgency to start cytotoxic therapy.

J Immunol. 2009 Mar 1;182(5):2859-67. IL-21 mediates suppressive effects via its induction of IL-10. Spolski R, et al Bethesda, NIH, USA

- IL-21 is a pleiotropic cytokine that is required for normal Ig production.
- IL-21 overexpression decreases specific Ab production
- IL-21 regulates immune responses at least in part by inducing IL-10 and reveal *unanticipated immunosuppressive* actions for this cytokine.

1: Rheumatology (Oxford). 2008 Sep;47(9):1379-83. Epub 2008 Jun 27.

Comment in:
Rheumatology (Oxford). 2009 Apr;48(4):451-2 author reply 452-3.

Prevalence, serological features, response to treatment and outcome of critical peripheral ischaemia in a cohort of lupus patients.

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OBJECTIVE: This study addresses the issue of risk factors and management of critical peripheral ischaemia (CPI) and gangrene in SLE and proposes rituximab as a novel therapy. METHOD: We conducted a retrospective study of 485 patients with SLE attending a UK tertiary referral centre, followed up over 27 yrs. Demographics, clinical features, serological features, treatment and outcome data were assessed. RESULTS: Seven out of 485 patients (1.4%) had evidence of gangrene or CPI with onset at any stage of SLE disease from presenting feature to 27 yrs after SLE onset, aPL and LAC were over-represented in the CPI patients. All had active SLE at the time of CPI. All seven were treated with intravenous (IV) epoprostenol infusion and aPL-positive patients were anti-coagulated. One patient failed to respond to this treatment and to IV calcitonin gene-related peptide but responded to B-cell depletion therapy using rituximab. Five out of the seven patients suffered digit loss with auto-amputation. CONCLUSION: CPI is a rare but potentially devastating complication of SLE associated with aPL, LAC and active SLE. B-cell depletion therapy with rituximab may be an option in severe ischaemia not improving with IV epoprostenol.

Tx médula

1: Blood. 2009 Jan 1;113(1):214-23. Epub 2008 Sep 29.

Comment in:
Blood. 2009 Jan 1;113(1):2-3.

Depletion of autoreactive immunologic memory followed by autologous hematopoietic stem cell transplantation in patients with refractory SLE induces long-term remission through de novo generation of a juvenile and tolerant immune system.

Alexander T, Thiel A, Rosen O, Massenkeil G, Sattler A, Kohler S, Mei H, Radtke H, Gromnica-Ihle E, Burmester GR, Arnold R, Radbruch A, Hiepe F.

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Clinical trials have indicated that immunoablation followed by autologous hematopoietic stem cell transplantation (ASCT) has the potential to induce clinical remission in patients with refractory systemic lupus erythematosus (SLE), but the mechanisms have remained unclear. We now report the results of a single-center prospective study of long-term immune reconstitution after ASCT in 7 patients with SLE. The clinical remissions observed in these patients are accompanied by the depletion of autoreactive immunologic memory, reflected by the disappearance of pathogenic anti-double-stranded DNA (dsDNA) antibodies and protective antibodies in serum and a fundamental resetting of the adaptive immune system. The latter comprises recurrence of CD31(+)CD45RA(+)CD4(+) T cells (recent thymic emigrants) with a doubling in absolute numbers compared with age-matched healthy controls at the 3-year follow-up (P = .016), the regeneration of thymic-derived FoxP3(+) regulatory T cells, and normalization of peripheral T-cell receptor (TCR) repertoire usage. Likewise, responders exhibited normalization of the previously disturbed B-cell homeostasis with numeric recovery of the naive B-cell compartment within 1 year after ASCT. These data are the first to demonstrate that both depletion of the autoreactive immunologic memory and a profound resetting of the adaptive immune system are required to reestablish self-tolerance in SLE.

1: Lupus. 2009 Apr;18(5):387-93.

Cellular therapy of systemic lupus erythematosus.

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Immunoablation with autologous hematopoietic stem cell rescue has been used in over 1,300 autoimmune disease patients, around 150 with SLE. Some patients have experienced durable remissions with loss of autoantibodies, whereas others either did not respond or died as a result of the treatment. Prospective randomised trials are required and are being planned to establish the place for this potentailly curative strategy. Mesenchymal stem cells are in an exploratory phase for the treatment of acute autoimmune disease including SLE. The principle is that they home to inflammed tissue and exert an antiinflammatory paracrine effect.

ARTHRITIS & RHEUMATISM
Vol. 58, No. 12, December 2008,

Spliceosomal Peptide P140 for Immunotherapy of Systemic Lupus Erythematosus

Results of an Early Phase II Clinical Trial

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Objective. **To assess the safety, tolerability, and efficacy of spliceosomal peptide P140 (IPP-201101; sequence 131–151 of the U1-70K protein phosphorylated at Ser^{140}), which is recognized by lupus CD4+ T cells, in the treatment of patients with systemic lupus erythematosus (SLE).**

Methods. **An open-label, dose-escalation phase II study was conducted in two centers in Bulgaria. Twenty patients (2 male and 18 female) with moderately active SLE received 3 subcutaneous (SC) administrations of a clinical batch of P140 peptide at 2-week intervals. Clinical evaluation was performed using approved scales. A panel of autoantibodies, including antinuclear antibodies, antibodies to extractable nuclear antigens (U1 RNP, SmD1, Ro/SSA, La/SSB), and antibodies to double-stranded DNA (anti-dsDNA), chromatin, cardiolipin, and peptides of the U1-70K protein, was tested by enzyme-linked immunosorbent assay (ELISA). The plasma levels of C-reactive protein, total Ig, IgG, IgG subclasses, IgM, IgA, and IgE, and of the cytokines interleukin-2 and tumor necrosis factor α were measured by ELISA and nephelometry.**

Results. **IgG anti-dsDNA antibody levels decreased by at least 20% in 7 of 10 patients who received 3 × 200 μg IPP-201101 (group 1), but only in 1 patient in the group receiving 3 × 1,000 μg IPP-201101 (group 2). Physician's global assessment of disease activity scores and scores on the SLE Disease Activity Index were significantly decreased in group 1. The changes occurred progressively in the population of responders, increased in magnitude during the treatment period, and were sustained. No clinical or biologic adverse effects were observed in the individuals, except for some local irritation at the highest concentration.**

Conclusion. **IPP-201101 was found to be safe and well tolerated by subjects. Three SC doses of IPP-201101 at 200 μg significantly improved the clinical and biologic status of lupus patients.**

Clinical trial approval no. 143/14.06.2006 (Bulgaria).

Supported by ImmuPharma France, an affiliate of ImmuPharma PLC, as part of a full clinical development program.

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1: J Immunol. 2008 Sep 1;181(5):3243-51.

The suppression of murine lupus by a tolerogenic peptide involves foxp3-expressing CD8 cells that are required for the optimal induction and function of foxp3-expressing CD4 cells.

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A peptide, designated human CDR1 (hCDR1), that is based on the CDR1 of an anti-DNA Ab ameliorates systemic lupus erythematosus (SLE) in murine models via the induction of CD4(+)CD25(+) regulatory T cells (Tregs). In the present study, the involvement of CD8 Tregs in the mode of action of hCDR1 was investigated in SLE-afflicted (NZB x NZW)F1 mice and in SJL mice following immunization with the lupus-inducing anti-DNA mAb that bears a common Id, 16/6Id. Treatment with hCDR1 up-regulated Foxp3-expressing CD8(+)CD28(-) Tregs in association with clinical amelioration of lupus manifestations. Furthermore, the in vivo depletion of the latter cells diminished the clinical improvement and the inhibitory effects of hCDR1 on the secretion of IFN-gamma and resulted in the up-regulation of IL-10. However, the stimulatory effect of hCDR1 on the secretion of TGF-beta was not affected by the CD8 Tregs. In the absence of CD8 Tregs, CD4(+)CD25(+) Tregs were unable to expand in the hCDR1-treated mice, and the expression of Foxp3 was reduced, thereby interfering further with the suppressive function of CD4(+)CD25(+) Tregs as determined in the in vitro assays. However, CD8 cells from hCDR1-treated mice that were adoptively transferred into SLE-afflicted mice led to up-regulation of CD4(+)CD25(+) cells with intensified Foxp3 expression in the recipient mice. Thus, a functional link between two subsets of Tregs is demonstrated in which CD8(+)CD28(-) Tregs are required for both the optimal expansion and function of lupus ameliorating hCDR1-induced CD4(+)CD25(+) Tregs.

1: Arthritis Rheum. 2008 Aug;58(8):2470-80.

Abetimus sodium for renal flare in systemic lupus erythematosus: results of a randomized, controlled phase III trial.

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OBJECTIVE: To investigate whether treatment with abetimus delays renal flare in patients with lupus nephritis. Secondary objectives included evaluation of the effect of abetimus on C3 levels, anti-double-stranded DNA (anti-dsDNA) antibody levels, use of high-dose corticosteroids and/or cyclophosphamide, and major systemic lupus erythematosus (SLE) flare. METHODS: We conducted a randomized, placebo-controlled study of treatment with abetimus at 100 mg/week for up to 22 months in SLE patients. Three hundred seventeen patients with a history of renal flare and anti-dsDNA levels >15 IU/ml were randomized to a treatment group (158 abetimus, 159 placebo); 298 (94%) were enrolled in the intent-to-treat (ITT) population (145 abetimus, 153 placebo), based on the presence of high-affinity antibodies for the oligonucleotide epitope of abetimus at baseline screening. RESULTS: Abetimus did not significantly prolong time to renal flare, time to initiation of high-dose corticosteroid and/or cyclophosphamide treatment, or time to major SLE flare. However, there were 25% fewer renal flares in the abetimus group compared with the placebo group (17 of 145 abetimus-treated patients [12%] versus 24 of 153 placebo-treated patients [16%]). Abetimus treatment decreased anti-dsDNA antibody levels ($P < 0.0001$), and reductions in anti-dsDNA levels were associated with increases in C3 levels ($P < 0.0001$). More patients in the abetimus group experienced > or =50% reductions in proteinuria at 1 year, compared with the placebo group (nominal $P = 0.047$). Trends toward reduced rates of renal flare and major SLE flare were noted in patients treated with abetimus who had impaired renal function at baseline. Treatment with abetimus for up to 22 months was well tolerated. CONCLUSION: Abetimus at 100 mg/week significantly reduced anti-dsDNA antibody levels but did not significantly prolong time to renal flare when compared with placebo. Multiple positive trends in renal end points were observed in the abetimus treatment group.

1: Arthritis Rheum. 2008 Aug;58(8):2488-97.

Anti-DNA Ig peptides promote Treg cell activity in systemic lupus erythematosus patients.

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OBJECTIVE: Treg cells oppose autoreactive responses in several autoimmune diseases, and their frequency is reduced in systemic lupus erythematosus (SLE). In murine lupus models, treatment with anti-DNA Ig-based peptides can expand the number of Treg cells in vivo. This study was undertaken to test the possibility that functional human Treg cells can be induced by exposure to anti-DNA Ig-based peptides. METHODS: Peripheral blood mononuclear cells were isolated from 36 lupus patients and 32 healthy individuals matched for ethnicity, sex, and age. Short-term culture experiments in the presence of several independent stimuli including anti-DNA Ig peptides were followed by flow cytometric analysis for identification of CD4+,CD25(high) T cells, cell sorting for in vitro suppression assays, and analysis of correlations between the expression of forkhead box P3 (FoxP3) and serologic and clinical characteristics of the SLE patients. RESULTS: The number of in vitro CD4+,CD25(high) T cells increased after culture with anti-DNA Ig peptides in the SLE patients, but not in the controls. The expanded CD4+,CD25(high) T cells required FoxP3 for cell contact-mediated suppression of proliferation and interferon-gamma production in target CD4+,CD25- T cells. The induction of FoxP3 in SLE Treg cells occurred only in seropositive patients, and was correlated with anti-DNA and IgG serum titers. CONCLUSION: These results suggest a new modality to reverse the functional deficit of Treg cells in SLE patients with positive autoimmune serology, and identify a new strategy to enhance immunoregulatory T cell activity in human SLE.

1: Arthritis Rheum. 2008 Aug;58(8):2453-9.

Association of plasma B lymphocyte stimulator levels and disease activity in systemic lupus erythematosus.

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OBJECTIVE: To determine the association of plasma B lymphocyte stimulator (BLyS) levels, immunosuppressive therapy, and other clinical parameters with disease activity in systemic lupus erythematosus (SLE). METHODS: Two hundred forty-five SLE patients were evaluated prospectively over a 2-year period at 4 centers. Assessments were performed every 3-6 months. Univariate analysis was used to determine the association among the Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) version of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, serum anti-double-stranded DNA (anti-dsDNA), and plasma BLyS levels. A multivariate repeated-measures model incorporating immunosuppressive therapy was utilized. RESULTS: Ninety-two percent of the patients were female. Sixty-seven percent were white, 31% African American, and 2% Asian (all of these groups may include Hispanic). Mean values at baseline were as follows: age 41.5 years, disease duration 8.1 years, SELENA-SLEDAI 3.3 (median 2, range 0-18), BLyS 5.57 ng/ml, IgG 1,439 mg/dl, C3 104.4 mg/dl, and C4 21.3 mg/dl; among those positive for anti-dsDNA, the median titer was 1:40 (range 1:10-1:1,280). Univariate analysis showed that plasma BLyS levels were associated with anti-dsDNA titers (P = 0.0465) and SELENA-SLEDAI scores (P = 0.0002). In multivariate analyses, a greater increase in the SELENA-SLEDAI score from the previous visit was associated with higher BLyS levels at the previous visit (P = 0.0042) and with a greater increase in the BLyS level from the previous visit (P = 0.0007). CONCLUSION: The findings of association between a greater increase in the BLyS level from the previous visit and a greater increase in the SELENA-SLEDAI score at the subsequent visit, and between an elevated BLyS level at the previous visit and a greater SELENA-SLEDAI score at the subsequent visit, demonstrate a relationship between circulating BLyS levels and SLE disease activity. These results lend support to the notion that BLyS is a candidate for therapeutic targeting in SLE.

1: Lupus. 2009;18(7):586-96.

Suppression of murine SLE by oral anti-CD3: inducible CD4+CD25-LAP+ regulatory T cells control the expansion of IL-17+ follicular helper T cells.

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Lupus is an antibody-mediated autoimmune disease. The production of pathogenic, class switched and affinity maturated autoantibodies in lupus is dependent on T cell help. A potential mechanism of disease pathogenesis is a lack of control of pathogenic T helper cells by regulatory T cells in lupus. It has been repeatedly shown that the naturally occurring CD4+CD25+ regulatory T cells in lupus prone mice and patients with SLE are defective both in frequency and function. Thus, the generation of inducible regulatory T cells that can control T cell help for autoantibody production is a potential avenue for the treatment of SLE. We have found that oral administration of anti-CD3 monoclonal antibody attenuated lupus development and arrested on-going disease in lupus prone SNF1 mice. Oral anti-CD3 induces a CD4+CD25-LAP+ regulatory T cell that secrets high levels of TGF-beta and suppresses in vitro in TFG-beta-dependent fashion. Animals treated with oral anti-CD3 had less glomerulonephritis and diminished levels of anti-dsDNA autoantibodies. Oral anti-CD3 led to a downregulation of IL-17+CD4+ICOS-CXCR5+ follicular helper T cells, CD138+ plasma cells and CD73+ mature memory B cells. Our results show that oral anti-CD3 induces CD4+CD25-LAP+ regulatory T cells that suppress lupus in mice and is associated with downregulation of T cell help for autoantibody production.

1: Arthritis Rheum. 2008 Jul;58(7):2098-104.

Failure of oral atorvastatin to modulate a murine model of systemic lupus erythematosus.

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OBJECTIVE: Inhibitors of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase enzyme (statins) are cholesterol-lowering drugs that have shown promise as therapeutic agents in various animal models of autoimmune disease. The results of initial clinical trials with statins in multiple sclerosis and rheumatoid arthritis have also been encouraging. In this study, we attempted to treat a widely studied murine model of spontaneous systemic lupus erythematosus (SLE) with atorvastatin. METHODS: (NZB x NZW)F1 (NZB/NZW) mice received daily oral doses of atorvastatin for 20 weeks. The mice were monitored weekly for survival and proteinuria. Anti-double-stranded DNA (anti-dsDNA) antibody levels in sera were determined by enzyme-linked immunosorbent assay (ELISA). T lymphocyte cytokine production in vitro, as well as cytokine levels in vivo, were measured by ELISA. T cell proliferation was assessed by thymidine incorporation assay. Serum cholesterol levels were determined using a standard fluorometric assay. Kidney tissue was harvested and evaluated for pathologic changes. RESULTS: In NZB/NZW mice, oral atorvastatin had significant effects on T cell proliferation and cytokine production in vitro. Atorvastatin also induced significant increases in serum levels of interleukin-4. However, atorvastatin treatment in NZB/NZW mice had no significant impact on proteinuria, survival, serum anti-dsDNA antibody and cholesterol levels, or extent of renal disease. CONCLUSION: Monotherapy with oral atorvastatin has no protective effects in a murine model of spontaneous SLE. The efficacy of atorvastatin in human SLE remains to be determined.