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NOVELTIES IN DERMATOLOGY

Psoriatic Arthritis: An Update☆

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Abstract Advances in our understanding of the pathogenesis of psoriatic arthritis and clinical aspects of the disease justify the present review. Studies have identified common inflammatory pathways related to the innate immune response, such as the IL-12/IL-23 axis, along with numerous genes that affect susceptibility to both diseases and influence phenotypic development. Interest has grown in biomarkers that can be used for early diagnosis or prognosis or to predict joint destruction and the response to treatment. Recent reports describe important differences between the effects of disease-modifying antirheumatic drugs and biologics on the process of new bone formation. Other issues that have been discussed include the need for reliable screening methods, particularly for early detection of oligoarticular arthritis, and for protocols to guide referral to specialists, especially in newly created multidisciplinary practices.

PALABRAS CLAVE
Psoriasis;
Artritis psoriásica;
Multidisciplinar;
Tratamiento

Actualización en artritis psoriásica

Resumen En los últimos años se ha ampliado el conocimiento de aspectos clínicos y patogénicos de la artritis psoriásica, que justifican la presente revisión. Se han identificado vías comunes de activación de la respuesta inflamatoria relacionada con la inmunidad innata, como el eje IL12/IL23 y numerosos genes determinantes de la susceptibilidad a ambas enfermedades, y diferencias en el fenotipo. El desarrollo de biomarcadores de diagnóstico precoz, pronósticos y predictivos de la destrucción osteoarticular y la respuesta al tratamiento son también de interés creciente. Recientemente se han descrito también diferencias importantes en la respuesta sobre el proceso de neoformación ósea entre FAME y biológicos. Asimismo, se ha puesto de manifiesto la necesidad de disponer de métodos de cribado fiables, en especial para identificar precozmente las formas oligoarticulares, y establecer criterios de derivación prácticos que permitan ofrecer una atención especializada, principalmente en el contexto de unidades interdisciplinares de nueva creación.

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Psoriatic arthritis (PsA) is an inflammatory, progressive, and often destructive arthritis associated with psoriasis. Diagnosis can be difficult as the disease has a variety of presentations often indistinguishable from other joint diseases such as osteoarthritis and gout.

Severe arthritis can be observed in the absence of psoriasis while very mild arthritis may occur in patients with moderate or severe psoriasis. Thus, a high degree of clinical suspicion, screening of patients with psoriasis, and combined evaluation by dermatologists and rheumatologists are essential to arrive at a diagnosis.

Early diagnosis of the disease and a targeted treatment from the start may help prevent long-term complications, joint destruction, and patient dependence. The availability of biological agents has equipped the specialists responsible for treating this disease with the necessary tools for its treatment. It is therefore more important than ever that efforts are pooled to improve early diagnosis.

Progress in Understanding the Pathophysiology of Psoriatic Arthritis

Common Pathophysiologic Pathways for Skin and Joint Diseases

PsA is a musculoskeletal disease that occurs in association with psoriasis. Although some susceptibility genes are common to both diseases, there are also many genetic differences. The psoriatic phenotype appears to be mediated by the susceptibility allele *HLA-C*06*, giving rise to a clinical presentation in which skin involvement predominates, with limited and late joint involvement, whereas the allele *HLA-B* and above all the alleles *HLA-B27* and *HLA-B38* are associated with a clinical presentation with joint involvement, with onset at the same time as skin manifestations.[1] The different epidemiological patterns of presentation of psoriasis and PsA suggest common mechanisms as well as mechanisms unique to each condition, with a complex mix of genetic and acquired factors.[2] Most of the inflammatory pathways have already been reported in psoriasis and, using these as a basis, inflammatory models have been proposed for the joints. Thus, the presence of external factors acting on the epidermis could activate dendritic cells that migrate to regional lymph nodes where they could present antigens to naive T cells, which in turn could be activated to Th1 and Th17 cells by local production of interleukin (IL) 12/IL23.[3] Expression of CCR4, CCR6, and CXCR3 on the surface of these lymphocytes may allow them to migrate from the vascular endothelium once more towards the epidermis, where they carry out an effector role to produce more inflammatory interleukins and chemokines able to recruit other inflammatory cells. Recently, investigators have reported *CARD14* gene mutations which give rise to proteins present in the outermost layers of the epidermis with a capacity to constitutively activate nuclear factor kappa-B (NF-κB), thereby inducing the production of chemokines such as IL8.[4] There is also an increase in the number of lymphocytes in the joints, triggering a local inflammatory response and inducing osteoclastogenic processes. This occurs through the receptor activator of NF-κB ligand (RANKL), the cytokine responsible for activating RANK, present in osteoclasts.[5]

Angiogenesis is an important component in the pathogenesis of both arthritis and psoriasis. Thus, tumor necrosis factor (TNF), IL8, IL18, and IL17 induce the production of vascular endothelial growth factor, Ang1, and Ang2, with the capacity to induce the formation of neovessels in the skin or synovium. Indeed, anti-TNF therapies have been shown to be effective at inhibiting this process in both domains.[6,7]

IL12, IL23, and IL17 have been shown to play a part in the pathogenesis of arthritis and psoriasis, for example, through clinical trials conducted with their corresponding inhibitors, ustekinumab, ixekizumab, and brodalumab, respectively.[3,8,9]

Genetics: Genotype-Phenotype Associations

In recent years, advances in our knowledge of the genes implicated in the pathogenesis of psoriasis and PsA have been made possible by the Genome Wide Association Scan (GWAS) studies. These have identified gene mutations implicated in the epidermal barrier (*LCE3*, *GJB2*, *DEFB4*) and genes involved in innate *(TNFAIP3*, *TNIP1*, *NFKBIA*, *TYK2*, *FXBXL19*) and acquired (*TRAF3IP2*, *IL23A*, *IL23R*, *IL4*, *IL13*) immune response.[10] Recently, 15 new susceptibility genes have been identified from a study of 10 588 patients with psoriasis and 22 806 controls. Some of the new genes identified are common to other autoimmune diseases and include genes implicated in the regulation of T-cell function (such as *RUNX3*, *TAGAP*, and *STAT3*). Other genes participate in innate immunity, including genes for interferon-mediated antiviral response (*DDX58*), macrophage activation (*ZC3H12C*), and NF-κB activation (*CARD14* and *CARM1*).[11] A model predictive of the risk of developing psoriasis has also be proposed using 10 susceptibility loci, which account for 11.6% of genetic variability.[12]

In the case of pustular psoriasis, a homozygous mutation at *IL36RN*, a gene that encodes the IL36 receptor antagonist, gives rise to an inactive antagonist that cannot bind efficiently to its receptor, leading to an increase in secretion of proinflammatory cytokines.[13]

Genotype-phenotype correlation studies have enabled the identification of associations between mutations in *LCE3D* and more severe psoriasis phenotypes, association between nail involvement and *IL1RN*, and the presence of PsA with mutations at the *IFIH1* locus.[14]

The search for specific susceptibility genes for PsA has confirmed the association of *HLA-C*, *IL22B*, *IL23R*, and *TRAG3IP2* with PsA; of *L28RA*, *TNIP1*, *IL23A*, and *RNF114* with psoriasis; and of new loci with both psoriasis and PsA (1p22, 5p13, 8q22, 14q12).[15] GWAS studies have enabled a specific signal to be identified in the *HLA-B/MICA* region (Elder et al., unpublished results). *HLA-B27*, *HLA-B38/39*, *TRAF3IP2*, *IL13* and some *MICA* alleles, among others, have been proposed as predisposing genes that can trigger PsA in individuals with psoriasis.[13]

In the case of interaction with environmental factors, a negative correlation has been found between smoking and the development of psoriasis or PsA.[16]